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SOME PROBLEMS IN SCANDINAVIAN OPHTHALMOLOGY 1969

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For a flourishing development of ophthalmology in Scandinavia too a sub specialization with intensified research into the separated fields is needed Such a sub specialization may be accomplished for given disease groups but it may also be based upon special exating diagnostic methods costly equipment spe cial forms of treatment or the need for special knowledge and experience The possibilities are manifold

How far it is advisable and desirable to carry the sub specialization must depend upon local conditions Even now a division is taking place into a limited number of departments having ophthalmosurgical equipment and others preponderantly for ophthalmomedical or ophthalmoneurological service having other but by now equally expensive equipment Laboratories for ophthalmic pathology have been established and so have orthoptic clinics glaucoma and tumour centres and ophthalmovirological advisory services Now an ophthal mochemical laboratory is a desired object Ophthalmogenetics is in good pro gress There is no saying where the sub specialization is going to end

The advantages of sub specialization are easy to see but it also involves a risk of spreading and isolating the units In some way or other the sub specia lities must be kept together not only mutually but also with other disciplines within medicine It is the great problem of our times to attain the outstanding within each field without losing the indispensable broad view

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A primitive method of integrating the units is centralization but unfortunately the centre is the very smallest part of the area of a circle If something is to be assembled in a centre other things have to be removed In that way *centralization carries within it the bud of its own annihilation* This simple fact is too often overlooked It is not possible to house everything in one place The integration must take place in some other way The ophthalmological tasks have to be divided between us Everybody must understand that something has to be ceded while concentrating on something else

True several more or less sub specialized eye departments may be collected in special eye hospitals Such complexes require a very large population basis and are indeed known mostly from certain million population towns And even in eye hospital complexes laboratories and other units may have to be housed outside In Scandinavia the most common practice is having eye departments in a large hospital system with other medical and surgical disciplines However this department system soon sets a limit to the facilities that each department has for sub specialization and the consequent extensions

To day the means of communication have reduced distances and geographic locations to a more subordinate role Even isolated eye clinics can take upon themselves special tasks for large geographic areas Accordingly the possibilities for sub specialization within the existing system are better than might be imagined at first sight if only a suited organization can be found A certain spreading of the sub specialized units may of course necessitate investments in equipment which would not have to be duplicated in a large unit However this drawback has to be viewed in the light of the great advantages In a speciality consisting of such relatively few persons there must be a certain number of attractive independent posts Otherwise recruiting within ophthalmology would be compromised Moreover we must avoid the risk of the development of science becoming too unified under a small number of chiefs

Once we let go the idea of geographic centralization and replace it by organized integration of the sub specialities we can direct our attention from each *individual country to the whole of Scandinavia Certain serious eye diseases* are so rare that real insight and experience of their treatment presupposes a concentration of the cases from several of the countries Therefore the considerations on ophthalmological sub specialization may with advantage be discussed before a Scandinavian forum

Sub specialization is bound to entail new problems for example in training for the Inter scandinavian diploma If the education in a sub specialized era is to be satisfactory service in one eye department cannot be considered sufficient Every candidate must do service in several departments and easier access to training in another Scandinavian country may become desirable

But just as important as the sub specializing is the necessity of not losing sight of the unity This further increases the importance of Acta Ophthalmolo

gica in collecting contributions from all sub specialities This will mark no rupture of its tradition which indeed has been to elucidate all facets of oph thalmology from practice to laboratory from supplements to case notes with out any demand of uniformity of the publications neither in form nor in ten dency

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DOUBLING OF THE PAPILLA

BY

P A LAMBA

The occurrence of complete or incomplete doubling of the optic nerve is rare Such an anomaly was seen by Gilbert Sourdille of Nantes in the course of enucleation Duke Elder (1964) described the duplication of the optic nerve as two discs each provided with retinal vessels seen on ophthalmoscopic examination in otherwise normal eye

The least marked condition is the presence of two sets of retinal vessels emerging from two separate depressions on the disc (Kubik 1925) but several cases have been recorded wherein an accessory disc usually smaller than the other is fused with the normal disc at its margins or is separated completely from it (Pesme 1951, Algen 1953 Alaerts 1954 and Rizzoli 1955) The condition is usually unilateral Collier (1958) observed an 8 year old girl with symmetric doubling of the disc in both eyes and a characteristic angio scotomatous picture

The aim of the present writeup is to add to ophthalmic literature another case of duplication of optic papilla with associated congenital abnormalities of rare occurrence

Case Report

A male aged 18 years presented in the Ophthalmic out patient department with the complaints of gross diminution of vision of right eye since childhood No history of sore eyes operation in the past

General examination showed that he possessed an asthenic built with height of 53 while his span was 54½ There was a patch of allopecia areata on the temporal regions on both the sides (Fig 1)

*) Received Aug 2nd 1967



Fig 1 A patch of alopacia aereta on the right temporal region

Ocular Examination

Both eyes showed a rotatory nystagmus Right eye showed a concomitant convergent squint of 15 with hypotropia (Fig ?)

Anterior Segment

Right Eye – There was a coloboma of the iris in the lower part from 5 to 7 O clock position and a rudimentary iris root could be seen on gonioscopy There was a poor response to mydriasis Cornea and the lens were normal

Left Eye – The pupil was round and normal in size It reacted well to light.

Visual acuity – Right eye – 6/60 *No improvement* with glasses

Left eye – 6 1? Improved to 6/6 with + 0 25 D Sph + 0 50 D Cyl 180°

Fundus Examination

Right eye (Fig 3 a) The media was clear Disc was horizontally oval and was normal in size and colour The retina and the blood vessels in the upper half of the fundus were normal The lower quadrant of the fundus showed a coloboma of choroid There was a marked pigmentary disturbance and glial tissue proliferation at the margins of the coloboma



F Right c nvergent squint with coloboma of right iris in lower part

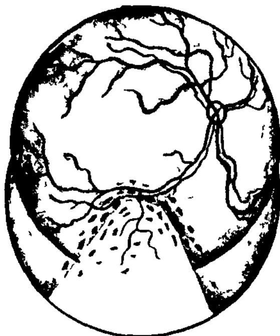


Fig 3 a
Fundus picture (right eye) Coloboma of choroid in lower quadrant

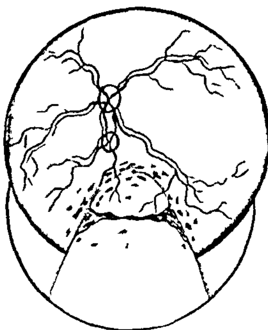


Fig 3 b
Fundus picture (left eye) Double optic disc with a separate vascular three
A coloboma of choroid is seen in the lower part

Macular area showed stippling and fine pigmentary disturbance Foveal reflex was dull and distorted

Left Eye – The media was clear The fundus exhibited a double disc The upper one normal in size shape and colour and showed normal emergence of the blood vessels The duplicating disc was smaller in size and was placed inferiorly about one disc diameter away This disc showed a separate vascular tree with physiological excavation The vascular trees of the two discs showed intercommunications Still inferiorly was placed a deadwhite area of sclera extending from just below the disc downwards and slight outwards towards the periphery widening as it proceeded in its course The edges were well defined and the surface slightly depressed and showed rudimentary choroidal vessels ridges of choroidal pigment and retinal vessels coursing over it (Fig 3 b)

X Ray Examination revealed that the optic foramen on the left side was double than the right side The left normal was smaller than the corresponding right while the left anomalous had a dense osseous ring (Fig 4)

Discussion

A division of the optic nerve into two strands have been noted as a rare anomaly The division of the optic nerve into several fasciculi occurs normally in some teleostean fishes In a few species like *Ameiurus Misgurnus & Polypnus* the optic nerve divides into as many as a dozen strands so that is enters the eye in multiple rootlets with a corresponding number of optic discs Elschnig (1914) on autopsy in a 66 year old female patient found two optic nerves on the right side and one was located above the other



Fig 4

Roentgenogram Arrow points to double optic foramen on left side – the two being separated by bony spicule

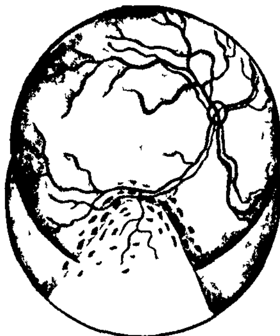


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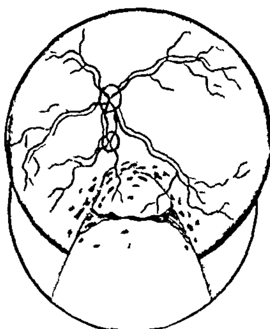


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No hereditary data or details of associated ocular anomalies had been available till the report of Collier (1958) Case reports by Kubik (1925) & Gallo et al (1952) only suggested the presence of a supernumery papilla in those patients while trying to differentiate it from abnormal retinal vessels and inferior parapapillar coloboma

Pesme (1951), Loushine (1952) Algan (1953) and Alaerts (1954) only gave a clinical description of the cases of double disc The presence of a myopic refraction in such patients was observed by Pesme (1951) and Jivkov (1961) while my patient shows a hypermetropic refraction

Rizzoli (1955) confirmed the presence of double optic disc in 45 years male patients by the presence of double blind spot The presence of characteristic angio scotomatous picture with symmetrical doubling of the optic disc was described by Collier (1958) The patient under consideration showed the presence of double optic foramen on the left side (on X Ray examination) confirming that the optic nerves have entered separately into the cranial cavity (Fig 4)

Only Jivkov (1961) described the presence of associated general abnormalities like cryptorchism obesity and hypogenitalism The patient observed by me exhibited an asthenic built with span more than height and the presence of allopacia aereta on the temporal regions on both sides

The presence of associated ocular abnormalities like congenital ptosis with exotropia on one side iris anomalies like pupillary ectopy and congenital lenticular opasities have been observed by Collier (1958) so far The presence of rotatory nystagmus with convergent squint and iris and choroidal colobomata have not been observed so far as observed in this patient

I agree with the views expressed by Collier that there is a great difficulty in diagnosing this condition and that other congenital variations related to optic disc and atypical ectatic colobomas should be well considered before diagnosing this rare condition The diagnosis of duplication of papilla should be made only when there are two separate vascular trees of the retina confirmed by scotometry or X-ray examination for the size of the optic foramen

Summary

The aim is to record a rare case of duplication of the optic papilla Still rarer is the association of such a congenital anomaly with the presence of coloboma of choroid (bilateral) and coloboma of iris The presence of double optic nerve was suggested by an independant vascular tree and confirmed by the roentgenogram examination which clearly showed two optic foramen separated by a bony spicule

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Fig 1

Hospital group study of hypertension

Relative Frequency of *Fundal signs in advanced Hypertension as Compared to* Arteriosclerosis without Diastolic Hypertension and Controls (percent)

	Calibre Variation	A/V crossing changes	Haemorrhages Exudates	Papilloedema
Diastolic Hypertension (60 cases)	55	47	20	3
Arteriosclerosis without diastolic hypertension (56 cases)	23	14	6	0
Controls (84 cases)	3	3	1	0

rhages and exudates were found in 20 % of this group There were three cases with papilloedema

Within the limits of the criteria sought the most common combination of two signs was *a/v crossing change and calibre variation* the most common combination of three signs consisted of these signs together with haemorrhages *and/or exudates* while the most common combination of four signs included papilloedema These combinations may possibly indicate that the common line of clinical evolution is a/v crossing change and calibre variation followed by haemorrhages and exudates and finally papilloedema In 3 out of 12 cases showing haemorrhages and/or exudates there was neither calibre variation nor a v crossing changes These were cases of excessive hypertension of short duration This then represents an alternative line of clinical event in hyper tensive retinopathy

The method of examination was direct ophthalmoscopy by at least two examiners who after each examining the patient discussed the findings This method is *fairly satisfactory for papilloedema haemorrhages exudates* calibre variation and Gunn s sign *It is completely* unsatisfactory for estimation of vessel breadth straightness and tortuosity This is so because the former are signs de novo while the latter are but variations of normal appearances The latter were indeed also estimated in this hospital *group study but were discarded when it was appreciated* how falacious the findings were To estimate vessel width straightening and tortuosity it is essential to have a greater number of *controls* precise measurements minimum of bias maximum observer control both inter personal and intra personal These need fundal *photography and a*

EPIDEMIOLOGICAL STUDIES IN CERTAIN DISEASES OF THE FUNDUS OF THE EYE*

BY

I C MICHAELSON JERUSALEM

Hypertension

There are two questions which my remarks will deal with Do the changes in the fundus in hypertension arrange themselves in a recognizable sequence of events? What is the significance of each sign with regards to the progress for the general body state? There are two studies to which I wish briefly to refer with regards to these questions – a hospital group study and a population group study – and it will be shown that these studies are complementary to each other (Michaelson et al 1966)

Hospital group study

It comprises 200 hospitalized patients who were divided into 3 groups

(1) Patients with diastolic hypertension – 60 patients

(2) Patients with arteriosclerosis with diastolic hypertension – 56 patients

(3) Patients without hypertension and without arteriosclerosis – 84 patients

Results

The results are shown in table 1 It can be seen that both calibre variation and a/v crossing changes are rare in the control group Calibre variation was found in 55 % and a/v crossing changes in 47 % of the hypertensive group Haemor

Received December 12th 1967

* Bjerrum Memorial Lecture in the Danish Ophthalmological Society December 1967

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Vessel breadth and the number of vessels were measured more unconventionally A plastic frame with a circular aperture 15 mm in diameter was so placed on each side that the centre of the aperture lay over the centre of the optic disc At the edge of the plastic frame were made a mark opposite each of the four main quadrant arterioles and a different mark opposite all the other (minor) arterioles where they met the aperture edge (Fig 3) Technicians could then measure at this edge the arteriolar diameter and the number of minor vessels This procedure supplied the following measurements Total width of major vessels total width of minor vessels number of minor vessels Methods employing precise measurement of vessel width have been employed by Margerie & Boyd 1960 Hill & Dollery 1964 Aurell & Tiblin 1966

Results

Vessel narrowing is frequently associated with hypertension especially in young patients Calibre variation is associated with hypertension But these changes may be present in patients without hypertension and hypertensive patients may be without them Straightness is essentially an aging process not connected closely with hypertension Tortuosity is not significantly associated with hypertension Gunns sign is an aging process accelerated by hypertension

Diagnosis of hypertension

It is clear that the absence of any sign early or late does not enable us to

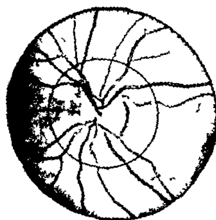


Fig 3
Marking of fundal photograph preparatory to measurement of vessel diameter and counting of minor vessels

population study in which individuals with hypertension are dispersed among individuals without hypertension A population study has its own built in control and there is little or no danger of bias The initial sign probably concerns changes in vessel width It is interesting to show how varied are the opinions regarding this sign (Fig 2) None of these authors were engaged in a population study

Population study

The population group that was studied consisted of 874 male subjects aged 40 and above 5 or 6 fundal photographs were taken of each of the 874 subjects The examining group had previously undergone intensive and statistically assessed *training of their capacity to diagnose the chosen signs with minimal* error among the observers At least two examiners were present at each session and they *independently assessed each individual step The examiners were not* aware of the identity of the subjects The conventional signs looked for were

Straightening	Calibre variation	Papilloedema
Tortuosity	a/v crossing changes	
Breadth	haemorrhages exudates	

Fig 2
Reports on the initial fundal change in hypertension
Initial retinal event in Hypertension

Keith & Wagner	(1937)	Mild narrowness of the vessels generally
Scheie	(1953)	Narrowness of the vessels generally Increased central light streak
Friedenwald & Ballantyne	(1930) (1937)	Broadening of the vessels generally with Tortuosity of perimacular vessels Increased central light streak
Salus	(1958)	Large vessels are usually normal while peripeheral vessels more or less constricted
Leishman	(1957)	(A) Broadening of the proximal extents of the vessels General narrowness of intermediate extents of vessels (B) Narrowness of the vessels generally

with a total major vessel diameter of 520 μ If this is so it may well be that the best use the ophthalmologist can be to the physician will be to supply him with information regarding the total width of the vascular bed at the level of the major or the minor vessels This can be supplied by a technician who photo graphs the disc area and makes the necessary measurements

Diabetic Retinopathy

Although we are all aware of the prevalence of retinopathy among diabetics and that the retinopathy often leads to blindness the shock of reading the stati stics remains 9/ % of diabetics develop retinopathy if they live the normal life span 17 % of all blindness in Massachussets in the years 1958–1959 was due to diabetes 10 % of all blindness in the United States is due to diabetes At St Paul s Rehabilitation Centre for new blinded adults Sullivan found that 30 % admitted had blindness due to the ocular complications of diabetes while only 10 % were due to glaucoma Similarly in Great Britain among the regi stered blind in the under 60 age group in 1962 diabetic retinopathy accounted for 11 3 % of the cases as compared with glaucoma s 4 6 % And here in Denmark diabetic retinopathy with 22 8 % heads the list of the causes of blindness

The evolution of the clinical pattern of this condition and the effect on it or the association with it of various parameters such as age duration degree of control type of control blood cholesterol pituitary ablation or a combina tion of these parameters are obviously of importance

The clinical evolution was first described by Ballantyne only 25 years ago In the light of general experience since this evolution might be somewhat modified There is however no difference of opinion regarding our general ignorance with respect to the rate of progress of the disease That is what is for each stage of the fundal pattern the percentage regression arrest and progres sion over say a 10 year period under the different circumstances of age dura tion and diabetes control These different circumstances may be grouped as follows

Young diabetics controlled	Duration 5 years or less
	Duration more than 5 years
Young diabetics not controlled	Duration 5 years or less
	Duration more than 5 years
Older diabetics controlled	Duration 5 years or less
	Duration more than 5 years
Older diabetics not controlled	Duration 5 years or less
	Duration more than 5 years

say that hypertension is not present The presence of haemorrhages exudates and papilloedema may justify the diagnosis of hypertension but not the presence of the early signs For example a total diameter width of the major vessels of 360 μ in the age group 40–49 years indicates in 37 % of cases hyper tension, but in 63 % there is no hypertension (Fig 4) At the other extreme among cases with a total width of 520 μ 85 % of them were without hyper tension but hypertension was present in 15 % of cases However the use of the fundal findings for the diagnosis of hypertension is not important in most cases The physician generally knows the diagnosis before the ophthalmologist examines the patient The physician is interested in knowing whether the retinal vessels are indicative of the general body state and prognosis

Prognosis in hypertension

If papilloedema haemorrhages or exudates are present information regard ing prognosis is available We may ask whether the early sign of nar rowing *is indicative of the prognosis In other words whether a patient with a* diastolic pressure of say 105 mm Hg and with a total major vessel diameter of 360 μ differs prognostically from a patient with the same diastolic pressure but

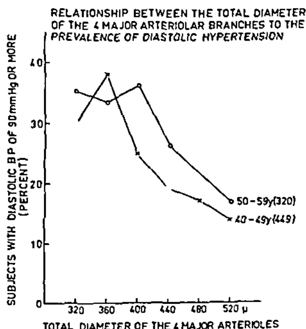


Fig 4

Relationship between the total diameter of the 4 major arteriolar branches to the prevalence of diastolic hypertension

387 patients have reportedly undergone pituitary ablation About half were improved about a quarter were worsened about one fifth died from the operation There are marked differences between the results of the 19 publications involved This may be partly due to techniques involved and partly due to differences with respect to the parameters of time of onset duration control etc as well as to stage of retinopathy That is why the construction of tables suggested is so important For example Rees (1965) using total hypophysectomy and stalk section has increased his improvement to 66 % as a result of demanding more strict indications A table showing the unoperated consequences with these criteria would be of value in assessing the worth whileness of an operation which results in diminished libido infertility dependence on supervised replacement therapy and despite which blindness may occur

The number of tables to be constructed according to the parameters suggested is 8 but this number will be greatly increased if we add to the parameters of age duration and control others such as the state of the vascular system elsewhere and the presence of unilateral proliferative stage This latter parameter is an exceedingly important one because it is often the patient who is blind in one eye because of proliferation and has stage 2 in the remaining eye who has to be considered for pituitary ablation

Although this investigation is an example of horizontal group study of diabetic patients there is one aspect which requires a general population study That is the diameter of the retinal veins There is an impression that preceding the micro aneurysm stage there is dilatation of the retinal veins Among the 874 subjects whose fundi were photographed as already described there were 40 diabetics The major and minor vein diameters were measured as these vessels crossed the circle in the same way as the arterial vessels had been measured This was also done in an equal number of controls The slides from the diabetics and controls were mixed so that the technician making the measurements was not aware of their identity There was no significant differences between the vein diameters in each group

The prevention of retinal detachment

There are 4 problems connected with retinal detachment which require population or group study the incidence the discovery of cases with pre detachment retinopathy the evolution of the pre detachment phase and the effect of preventive therapy

For each combination of circumstances the following information is required (Fig 5) There are quite a few reports on this matter especially with regards to proliferative stage (Beetham 1963 Caird & Garret 1963 Fischer 1966)

A pilot study is at present under way in Jerusalem investigating parameter group prognosis Each patient undergoes periodically a general medical examination including an ECG urine and blood tests The latter will *include* blood lipids blood insulin growth hormones (under supervision of Prof A M Cohen) *Periodical ophthalmological* examination will include visual acuity tonometry biomicroscopy ophthalmoscopy and in cases where necessary biomicroscopy with Goldmann s three mirror lens Each patient will have fundus photography done periodically Each fundus will be photographed separately the disc the macula and the four quadrants making a total of six photographs for each fundus each time Fluorescein photography is available and will be used if in the course of the study is found necessary

The group study embarked upon is essential if we *wish to study the effect* of treatment The evolution of the fundal picture is probably so dependent on age of onset *duration of diabetes, and possibly of the* diabetic control, that without the tabulated basic information we would not be able to properly plan a therapeutic experiment or assess its results For example it is important to remember that Beetham (1963) among 351 cases of proliferative retinopathy followed over a number of years found 35 patients in whom the condition became quiescent in time to preserve good vision

Between the report of Luft et alia (1955) and that of Rees et alia (1965)

Fig 5

Type of information required from each group of parameters

Condition of better eye on 1st examination	Number of patients	Regression (%)	Arrest (%)	Progression (%)
Normal		–	–	%
Stage 1		%	%	%
Stage 2				
Stage 3				
Stage 4				
Stage 5 (a)				
Stage 5 (b)				
Stage 5 (c)				

detachment among 50 000 new patients were observed in Liberia and Tanzania An incidence of 21 cases of retinal detachment among a total population of 11 million does not of course reflect the real incidence of the disease because of the habits of the population and the long distances to travel It is however an extremely low incidence despite these reservations A good assessment can however be made by considering the capitals only of these countries The size of the population in these towns is well known and the distances to the eye departments are small so that one can expect all or at least most the people suffering from eye disturbances to attend the hospitals

The combined population of Monrovia and Dar es Salaam is 150 000 Four out of the 21 patients with retinal detachment came from these towns During the 6 years observation this represents an annual incidence of 0 6 per 100 000 If this is compared with the 9 per 100 000 observed in Israel it can be seen that there is a large difference between the incidence of retinal detachment in Caucasian and Negro populations

The discovery and treatment of eyes with pre-detachment retinopathy

Patients with predetachment may be accidentally found in the clinic or may come with complaints of muscae or flashes or having little or no symptoms must be sought out and brought to examination Concerning the latter there are certain types of individuals that are liable to retinal detachment The following table lists the main types of patients found in retinal detachment cases their percentage incidence as noted in published reports their percentage incidence in cases occurring in Israel between 1956 and 1959 and the estimated number of patients of each type at risk in Israel in 1960

We are of course interested in the types of patients with a certain predo

Types of Individuals	Average % incidence of types in cases of detachment reported in world literature	Average % incidence of types in cases of detachment in Israel 1956–1959	Number of case at risk in Israel in 1960
Myopia less than 3 D	5	30	about 95 000
Myopia 5 D or over	5	40	about 95 000
Aphakia	10	11	7 000– 8 000
Myopia and aphakia	7	8	1 000
Second Eyes	0	1-	1 000

The incidence of retinal detachment

There is not much information in the literature regarding the incidence of retinal detachment I would like to discuss attempts to do so in Israel and two countries in Africa – Tanzania and Liberia

Israel

Beginning in January 1960 all the eye departments in Israel (now totalling 12 in number with 251 beds) notify each fresh case of idiopathic retinal detachment to a central office which has a permanent secretary for this and other purposes which I will shortly indicate Israel is a land of immigration and changing population The group considered is therefore limited to those who were in Israel on the 1st of January 1960 – 1 882 600 (Jewish population all ages) All Jewish immigrants since then and all non Jews were excluded from the statistics Each department sends to the central office each month a nominal role of fresh cases of retinal detachment which includes date of immigration into Israel From these lists the following are examples of the type of information that are available

1 Average incidence of cases with retinal detachment during the years 1960–1966 (per 100 000 of population) 8 58
2 Average percentage of detachments where 2nd eyes are involved 8 62
3 Average percentage of detachments where myopic aphakic eyes are involved 8 93

The lists do not include dischisis or secondary retinal detachment Traumatic detachment for our purposes is diagnosed if there has been a perforating injury hyphaema or a strong contusion injury to the eye or its close neighbourhood This is probably a true indication of the incidence of second eye retinal detachment Practically all clinics give a higher percentage than this but it is clear that the more a clinic has a reputation for performing retinal detachments the more likely is it to have many second eye detachments and it is from such clinics that publications are most likely to appear

Africa

The eye clinic in Monrovia (the only one in Liberia) serves a population of 1 5 million During the 6 years 1961–1966 about 30 000 new patients were examined 11 cases of idiopathic retinal detachment were seen during these years The eye clinic in Dar es Salaam (the only one in Tanzania) serves a population of 9 5 million During the 4 years 1963–1966 about 20 000 new patients were examined 10 cases of idiopathic retinal detachment were seen during these years Putting these figures together only 21 cases of retinal

detachment among 50 000 new patients were observed in Liberia and Tanzania An incidence of 21 cases of retinal detachment among a total population of 11 million does not of course reflect the real incidence of the disease because of the habits of the population and the long distances to travel It is however an extremely low incidence despite these reservations A good assessment can however be made by considering the capitals only of these countries The size of the population in these towns is well known and the distances to the eye departments are small so that one can expect all or at least most the people suffering from eye disturbances to attend the hospitals

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minance in retinal detachment whose population (being the "population at risk) is low in the general population and who are likely to be in attendance at an ophthalmic department

With these considerations in mind the following types of patients are being especially examined for the presence of pre detachment retinopathy

(1) The "second eye" in all cases of retinal detachment
(2) All cases of aphakia with myopia
(3) All cases presenting symptoms suggestive of detachment retinopathy

In most of the departments involved in this study special clinics have been set up for the investigation of these type of patients

Effect of preventive therapy

Preventive retinal detachment may be said to have been begun on an intensive scale in Israel in January 1960 During the 1960–66 period the following data from each department are being received

(a) The number of preventively treated eyes
(b) The number of "second eyes" treated preventively
(c) The number of aphakic myopic eyes treated preventively

Results

Despite the 1068 eyes that have been preventively treated since 1960 (1960–1966 incl) there is no clear change in the incidence of retinal detachment in the population the necessary corrections having been made for increase and ageing of the population This may mean that the latency between hole discovery and detachment formation is longer than the period under observation in which case the effect of the closure of so many holes on the incidence of retinal detachment may not be felt for a number of years If this is not so it must mean that only a small proportion of the eyes treated would if untreated have developed retinal detachment and that the number of cases treated forms only a small proportion of the cases present in the population If the first proposition is correct the incidence of retinal detachment should fall after several more years If the latter proposition is correct there is little to be excepted from preventive therapy using the methods of case finding and selection in use at present

Besides the unknown but probably years long latency between hole formation and retinal detachment there are other chiefly organizational factors which indicate that the expected fall in incidence will gather momentum after a few years

To determine the natural history of the pre-detachment phase of retinal detachme

To achieve this as many as possible cases of detachment retinopathy in t pre detachment phase have completed with respect to them an investigati form which is common to all the departments in the country This includ all cases that have had preventive treatment and all cases that had a retir detachment operation (2nd eyes only) It also includes cases that have h neither preventive treatment or a detachment operation

In this sheet are noted data regarding history symptomatology and ophtha moscopic changes which may be relative to the case Information regardi any preventive measures carried out is noted Details regarding the state the vitreous and changes in the funds including pigmentation choroic changes lattice formation cystoid degeneration and hole formation are arranged that they can be transferred to code sheets Each investigation fo is sent to the central office for abstraction of the information and immediat returned to the eye department which sent it After every new examination usually once a year – the investigation sheets are again sent to the cent office where the information of this new examination is taken note of T information on the code sheets will be analysed with respect to the problems the natural history of the pre detachment phase already detailed As this a country wide study it is possible to follow the development of changes ev if the patient change his place of attendance

General conclusion

Examples have been given of selected and unselected population studies three retinal diseases and their roles separately or combinedly are indicat The important role of unselected population studies is emphasised especi when the retinal appearances are not de novo but changes in appearar present in the normal retina

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LEBER s DISEASE III

BY

TOVE SEEDORFF

Summary

This paper reports part of a study aiming at completing previously published Danish families with Leber s disease and thereby at contributing a share in the discussion concerning the carrier rate The family in question comprises 59 persons distributed over 9 generations There is a high percentage of childless women in this family In the discussion of the value of the pedigree it is pointed out that owing to the sparse reproduction it is hardly possible to establish the carrier rate with a reasonable limit of error in such a pedigree in spite of its considerable size

Material and Method

The basis for collecting this material was afforded by references to hospital records for the patients of pedigree D in *Lundsgard s* thesis (1944) While registration of the family was in progress the Eye Department of the Copenhagen City Hospital reported that a patient with Leber s disease had been admitted and identified as a member of Lundsgård s family D In the new pedigree this patient is D 52 the only new case found in the present study Incidentally the material was supplemented as described in two previous papers (*Seedorff* 1968)

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Fig 1
Pedigree D

Position of Previous Authors Patients in the Pedigree
Jensen s No 15 who became Lundsgård s Case 45 is No D 14 in the present pedigree Lundsgård s Case 46 is D 16 her Case 47 is D 27 Case 48 is D 34 and Case 49 is D 40

Corrections to the 1944 Pedigree
In the sibship D 42–46 a girl has been added D 42 This girl born before her parents married was adopted during infancy by her maternal uncle D 27

Additions to the 1944 Pedigree
The youngest generations have been supplemented so that all children born up to and including 1960 are listed The year of birth year of manifestation and year of death are stated below the person symbols in so far as they are known Persons of the 6th generation and onwards were alive in 1960 if no year of death is stated The additions constitute 5 births in the 9th generation manifestation of the disease in D 52 carrier property in D 38 and childlessness in D 42 D 43 and D 44

Size of Pedigree
59 persons 31 females and 28 males

Reproduction
The shape of the pedigree depends upon the fertility in the female lines and upon the registration of descendants 10 childless women and 3 women whose possible descendants are unknown all in the right part of pedigree D make the pedigree lopsided

In the 5th generation 6 females were born 3 remained childless 1 may have unknown descendants

In the 6th generation 7 females were born 2 remained childless

In the 7th generation 8 females were born 4 remained childless and 1 may have unknown descendants

In the 8th generation 2 females were born neither was childless

In the 9th generation no females were born and the female lines are thus coming to an end

The cause of childlessness cannot be studied now D 5 died unmarried It is not known whether D 18 D 20 and D 21 ever married D 30 and D 33 have lived a long and childless life married to men of their own age D 41 died at 20 D 42 is married D 44 married D 54 after he had acquired the disease both being aware of the predisposition

Rate of Manifestation Among Males
A calculation may be made for the 5th and 6th generations in which the age

at manifestation ranged from 30 to 43 years (D 34 acquired the disease in 1936 the ages at manifestation in the other cases are shown in the pedigree)

In the 5th and 6th generation a total of 12 boys were born 9 of whom reached the age of 10 years The disease occurred in

33 % of the boys born in these two generations (4 out of 12)

44 % of the boys who attained the age of 10 years (4 out of 9)

25 % *of the boys born in the generations lived to be 60 without developing* the disease (3 out of 12) Among these men one became in his sister s words "almost quite blind because of old age (cf case histories D 29)

Rate of Manifestation Among Females

No ocular disease has been recorded among the female members of the family

Carriers

Calculation is not permissible in the first 3 generations of the pedigree as they were built up in ascending lines It is possible for the 4th and 5th generations which have remained unchanged since *Lundsgard s* study in 1944 These two generations comprise 9 females

0 patient
4 carriers
5 undeterminable
  2 females who may have unknown descendants D 11 and her daughter D 23
  3 females without descendants D 18 D 20 and D 21

The 6th generation which is under observation comprises 7 females who were distributed as follows in 1960

0 patient
1 carrier
3 undeterminable
  1 female with practically unknown descendants D 32
  2 females without descendants D 30 and D 33
3 undetermined The descendants of D 24 have to be kept under observation perhaps even until 1999 the descendants of D 28 until 1975 and the descendants of D 36 until 1989

Pedigree D includes 50 % undeterminable females of the 4th 5th and 6th generations (8 out of 16)

Non carriers

It is not possible to prove for any woman of the pedigree that she is not a carrier

Reliability of the Pedigree

The knowledge of the family members was renewed only back to sibship D 12-15 The names of the persons D 1-D 11 and D 17-D 23 are unknown to day The author had no intention to test the genealogical work which underlies the 1944 pedigrees only to acquire a sufficient knowledge of the family to have a basis for *following the descending female lineage* The sibship in the 4th generation is considered to be complete as Lundsgård is believed to have had the possibilities of complete recording In the lower part of the pedigree the sibships must be considered complete except for the de scendants of D 11 and D 32 There is little chance of finding these unknown descendants The name of D 23 is unknown to day she was born out of wedlock presumably in Copenhagen D 48 s parents emigrated to U S A and lived on Long Island

Recording Manifestation

There are no data regarding the vision of persons in the first 3 generations of the pedigree In subsequent generations too the symbols for persons with good vision have to be taken with reserve as no member was regularly exam ined until death One doubtful case D 29 is marked by a symbol for non affected

Case Histories

D 52 had a truly typical case of Leber s disease The development of the disease was observed in hospital so that here only an identification code will be given

D 52 H H C born 2 1 1923 Eye Department Copenhagen City Hospital 1961

D 28 stated in 1965 concerning D 29 that during the past few years he had in fact been completely blind because of old age The author visited D 29 in his home but he was in bed and his wife did not want to have him examined At that time D 29 was over 80 years of age and had been affected with his eye disease for some years

Discussion

The intention is to describe the family so fully as to avoid the use of the proband method for calculation of the carrier rate Therefore the procedure is first to record every member of the family *while they are children or young* people without eye disease and later to ascertain whether or not they have

acquired the disease The eye disease in D 52 appeared at a time when Lundsgård s notes about the family were lost and the new registration had not been completed It is questionable therefore whether D 52 is to be interpreted as a proband As a matter of fact this patient was used in 1961 as a proband case by the ophthalmologist who found him When Lundsgård s pedigree was published in 1944 he was 21 years of age and was marked in the pedigree as unaffected male Therefore he will not be considered a proband in the present study

The pedigree has a larger proportion of childless women than found in the general population The Statistical Tables for Denmark 1962 (Statistical Department) include tabulations showing how many women never bear children The tables sum up the number of women at various ages who have borne at least one child The percentages are calculated on the basis of the number of 15 year old females in the population It is apparent that among the generation born 1907–1908 a total of 74 7 % of women at the time when they reached the age of 47 had borne one child (actual number) Out of the generation born in 1924–1925 81 1 % will have borne one child when they reach the age of 47 (calculated number) The remaining portion when disregarding the mortality during the age range 15–47 years is that part of the women who never bear children Thus the percentage that never bear children is around 19–25 % Among the women born in family D during the period 1820–1920 nine out of 24 women were childless which must be considered a higher percentage than in the general population

This childlessness of course means that the material will become small Incidentally the 1–2 child principle means that more than one generation has to be observed before 2 male descendents are recorded In addition sparse reproduction and childlessness may well result in a poor registration of the family because there is no one to give the information concerning the few existing descendant lines Therefore families with sparse reproduction are difficult to record There may easily be a relatively large number of women who perhaps have unknown descendants and the category undeterminable may amount to 50 % as in the present pedigree This illustrates the obstacles to establishing whether the carrier rate among live born girls exceeds 50 %

When assessing the number of carriers and non carriers it is essential to pay regard to the difference in time needed for fulfillment of the criteria The criterion of carrier may have been fulfilled as early as about 40 years after the carrier s birth if only she has borne one son who acquires the disease at an early age The criterion of non carrier is not fulfilled until at the earliest about 80 years after her birth and in that case only if she has two male descendants who have lived to be 60 Among the 4 carriers in the 4th and 5th generations of pedigree D only two women (D 12 and D 15) have borne two sons attaining the age of 60 It was not until through her daughters that

D 9 got male descendants who lived to be 60 D 10 had only one male de scendant a son who lived to be 60 If among these women there had been merely one who fulfilled the criterion of non carrier her presence would have been weighty support to the view that carriers make up only 50 % of the carrier s daughters Since the calculations in pedigree D are done on the basis of only 9 women 5 of whom are undeterminable it must be considered unwise to draw any conclusion from the pedigree as it is now

Nevertheless it is of great interest that all four women whose male de scendants are known proved to be carriers Pedigree D is still of interest because it includes so many males of the youngest generations that the carrier property if present will become apparent as manifestation of the disease among the descendants of D 24 D 37 D 50 D 53 and D 28 all of whom have two or more male descendants and perhaps also among the descendants of D 36 and D 39 who have only one male descendant each D 32 whose descendants are practically unknown will presumably remain undeterminable In other words 5 or perhaps 7 out of 8 females will thus have shown whether or not they are carriers before the year of 2018 if only the descendants live long enough

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COMBINED GLAUCOMA AND CATARACT OPERATION

BY

OTTO FREDRIK KLOUMAN KRISTIANSAND NORWAY

The combination of a cataract operation with any of the usual antiglaucomatous procedures increases the risk of serious complications due to postoperative hypotony The risk should be greatly reduced however if fistulation could be made to start only gradually some time after the operation This may be attained by altering some small details in the suturing of the wound to assure *permanent suture track fistulation*

Suture track fistulation is usually the result of too deeply placed and/or too tightly tied silk sutures A nearly vertical incision probably increases this tendency as well as posterior gaping of the wound To secure fistulation I therefore have used a nearly vertical incision in the 12 o clock region with a deep *tight suture here At first the suture was placed deep intralamellar* later into the chamber In both events the suture has been tightened definitely more than usual to obtain suture track necrosis and evt posterior gaping of the wound To both sides the incision has been beveled with ordinary sutures at 10 and 2 o clock The sutures have been covered with a good conjunctival limbusbased flap and the conjunctival wound closed with silk sutures

The 12 o clock suture should be well behind the corneo conjunctival junction With a small anterior segment the incision therefore might have to be slightly *beveled away from the ciliary body Unduly tightening will cause the suture* to slough out The sloughing will always be outwards as the anterior scleral lip is the most resistant part of the wound

Davis & Geck Anacap surgical silk size 6–0 (black braided non capillary type B) has been used A smaller size will probably give less fistulation

Only 9 patients with open angle glaucoma have been operated the last 4 with a suture into the chamber The first cases had 2 and even 3 deep tight sutures inserted Luckily enough these extra sutures soon sloughed out without *visible fistulation The tension lowering effect of a single well functioning* fistula appears to be sufficient in most cases

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Received May 15th 1968

In the immediate postoperative period the eyes have been completely like eyes operated in the usual way The chamber has been deep from the first day Descemet wrinkling has been negligible Glaucoma medication including Diamox has been stopped at operation Atropine and steroid drops have been given for some weeks Fistulation could be seen from the 6th to the 8th day in most cases in 3 only after two weeks When fistulation begins this will lift up the conjunctiva so that it will not be eroded by the knot There has been no infiltration or redness around the filtering suture In one case a cystoid bleb has formed in the others only a pale thickening over the suture is seen

Results

Table I shows the VA and the IOP at operation and at the last examination Two weeks after operation the IOP ranged from 10 2 to 22 4 mm Hg (mean 14 1 mm) Three weeks later cases 3 and 8 had a transitory rise to 26 and 29 mm resp probably steroid induced Since then the IOP in all cases has remained stable at the same level as at the last examination

I cases 5 7 and 8 a fistulizing operation had been done years before The other eye was amaurotic or lost in cases 1 3 7 and 9 The visual field was heavily restricted in cases 3 4 6 and 9 Further deterioration has not taken place (Cases 1 2 and 6 are now dead) The visual gain might seem slight in some cases due to macular

Table I

Preoperative VA and IOP with medication and postoperative VA nd IOP without medication

Nr	Age	Preoperative VA	Preoperative IOP	Postoperative VA	Postoperative IOP	Follow up
1	80	Fct 2 m	40 mm	5/10 +	15 mm	17 Months
2	83	Hand mov	[illegible]	5 5 —	14 6	6
3	69	Fct 5 m	35	5/5	13 4	30
4	6	Fct 1 m	[illegible]	5 20	11 2	30
5	67	5 15	2[illegible]	5 5	17 8	29
6	78	Hand mov	29	5 0	12 7	8
7	81	Fct ½ m	30	Fct 1½ m	14 6	19
8	9	Light p	26	Fct 1½ m	14 6	18
9	4	Light p	24	5/5	14 6	13

Embarrassing nuclear cataract and other eye aphakic

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OTTO FREDRIK KLOUMAN KRISTIANSAND NORWAY

The combination of a cataract operation with any of the usual antiglaucomatous procedures increases the risk of serious complications due to postoperative hypotony The risk should be greatly reduced however if fistulation could be made to start only gradually some time after the operation This may be attained by altering some small details in the suturing of the wound to assure permanent suture track fistulation

Suture track fistulation is usually the result of too deeply placed and/or too tightly tied silk sutures A nearly vertical incision probably increases this tendency as well as posterior gaping of the wound To secure fistulation I therefore have used a nearly vertical incision in the 12 o clock region with a deep tight suture here At first the suture was placed deep intralamellar Later into the chamber In both events the suture has been tightened definitely more than usual to obtain suture track necrosis and evt posterior gaping of the wound To both sides the incision has been beveled with ordinary sutures at 10 and 2 o clock The sutures have been covered with a good conjunctival limbusbased flap and the conjunctival wound closed with silk sutures

The 12 o clock suture should be well behind the corneo conjunctival junction With a small anterior segment the incision therefore might have to be slightly beveled away from the ciliary body Unduly tightening will cause the suture to slough out The sloughing will always be outwards as the anterior scleral lip is the most resistant part of the wound

Davis & Geck Anacap surgical silk size 6-0 (black braided non capillary type B) has been used A smaller size will probably give less fistulation

Only 9 patients with open angle glaucoma have been operated the last 4 with a suture into the chamber The first cases had 2 and even 3 deep tight sutures inserted Luckily enough these extra sutures soon sloughed out without visible fistulation The tension lowering effect of a single well functioning fistula appears to be sufficient in most cases

Received May 15th 1968

From Statens Åndssvageforsorg Center II Ebberødgård
(Head P A Schwalbe Hansen) Birkerød Denmark

A CASE OF THE RUBINSTEIN TAYBI SYNDROME

BY

JENS FALBE HANSEN

In 1963 *Rubinstein and Taybi* published a report on seven children with mental retardation abnormal facial features and broad thumbs and great toes

The following year *Coffin* (1964) described six cases of the same syndrome and in 1965 *Taybi and Rubinstein* presented six new cases

This peculiar syndrome is of special interest to ophthalmologists because the patients all exhibit one or several characteristic ocular abnormalities

Case History

The case presented here is a 62 year old male who has spent most of his life in institutions for the mentally deficient He was the second child in a family in which there were two other normal children There is no history of parental consanguinity and both parents were normal In the family there is no record of other cases of mental deficiency Pregnancy and delivery were normal At the time of birth the mother was 25 years of age and the father 28 The baby was described as weak in the postnatal period but the nature of this weakness is not specified At 2 weeks he suffered from bilateral dacryocystitis probably cured by probing During early childhood he suffered from constipation and was supposed to have rachitis He also underwent an operation for inguinal hernia

His mental development was very slow He started saying a few words at the age of 4 years and at 6 his speech was described as more primitive than that of a 2 year old child He started walking at 4

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involvement but the subjective improvement in cases 7 and 8 has been much greater than these figures would indicate

All but No 4 had capsular glaucoma In two cases a large tuft of dense pigment accumulated at the inner site of the fistula probably adhering to the thread This unusual finding was taken as a sign of the heavy pigment dispersion in these eyes The tufts disappeared after some weeks

Discussion

By this method serious hypotony in the immediate postoperative period should be avoided *At the completion of the operation the eye is just as firmly* closed as after an ordinary cataract operation If the IOP has been high the eye should theoretically be even more firm than usual until fistulation ensues

Many will have objections to the leaving of a silk suture into the chamber I too had and therefore used only deep intralamellar sutures in the first cases A suture into the chamber probably entails no more risk than a deep suture with posterior gaping of the wound Fistulation should be more assured with a suture into the chamber In both cases the suture will recede somewhat outwards due to necrosis As long as the covering conjunctiva is not eroded *there should be no risk of epithelial ingrowth or infection If the suture sloughs* out the fistula will probably close but other harmful consequences should not be expected

It is well known that the glaucoma often will be easier to handle after removal of a cataractous lens even without fistulation Although this may have contributed to the reduced IOP in the operated cases the main tension lowering factor has probably been the clearly visible fistulation

Summary

Suture *track fistulation has been deliberately* used as a means of reducing the intraocular pressure in cases with combined glaucoma and cataract A method to assure such fistulation has been described Fistulation starts gradually some time after operation and serious hypotony in the immediate postoperative period is avoided

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Received November 25th 1968

The first medical report on the patient was written when he was 5 years old by the family physician The child was described as bashful but friendly

His motor achievements were not specified but he was described as weak and not being able to keep up with other children of the same age His peculiar broad thumbs and great toes were noticed and also his pupillary defect His testes were undescended and he had inguinal hernia probably bilateral

The next medical report was written when the patient was 10 years old His speech was quite good by then but in other respects his progress was poor He was classified as imbecile

During adult life he has suffered from various ailments At 37 tuberculosis of the right lung was diagnosed The lesion gradually healed during a couple of years Since the age of 54 he has suffered from recurrent pyelonephritis At 55 he had a bilateral inguinal herniotomy

Physical examination

Today at the age of 62 the patient weighs 37 kg and is 138 cm tall His mental retardation is pronounced but he is friendly and cooperative He is mostly sitting in a wheeling chair because of marked stiffness of the knee joints He



Fig 1



Fig 2

can walk a little but the gait is slow and clumsy and characterized by typical genu valgum

The head is slightly smaller than normal length 20 2 cm and width 15 8 cm The nasal bridge is broad and the nose is beaked (figs 1 and 2) A septal deviation is present The palate is normal and not highly arched The outer ears are quite big but without any anomalies Hearing is normal The skin is normal A soft systolic murmur is heard over the whole precordial area The spine is deformed as described under the roentgenographic examination There is bi



Fig 3

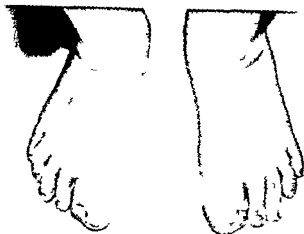


Fig 4

3

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Fig 1



Fig 2

The electroencephalogram is interpreted as diffusely abnormal without localization with low frequencies mostly in the occipital area

Roentgenographic examination of the spine shows a marked kyphoscoliosis with a maximum at the 9 11 thoracic vertebrae which are completely wedge shaped The heart and the lungs are normal The pelvis is slanting to the right and the collum femoris on both sides is in a marked valgus position The proximal phalanges of the thumbs are short wide and deformed The plane of *the interphalangeal joints is parallel to the longitudinal axis of the finger* (fig 5) The distal end of the ulna is mushroom shaped with an overdimensioned styloid process The proximal phalanges of the great toes are bifid and the distal phalanges completely duplicated (fig 6) The skull is only the size of a six year old child s but otherwise normal

Eye examination

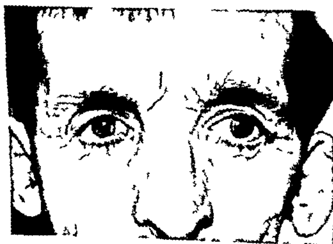
Visual acuity both eyes Light perception

There is a slight antimongoloid slant to the palpebral fissures the eyelids are normal

Fixation is very poor there are constantly slow nystagmoid horizontal movements of the eyes The motility is normal

There is a moderate exotropia about 15

Slit lamp examination both eyes The cornea is normal In the typical position downwards and inwards a total and complete coloboma of the *iris is* seen (fig 7) The lens is cataractous and completely opaque A small notch is seen at the lower nasal edge of the lens



Fig

lateral cryptorchidism Inguinal herniotomy has been performed on both sides The thumbs are wide and flexed in the terminal phalangeal region with outward displacement of the terminal phalanges (fig 3) The first toes are very broad with bifid nails (fig 4)



Fig 5



Fig 6

From the Finsen Laboratory Strandboulevarden 49 2100 Copenhagen Ø Denmark
Chief Professor M Faber

DEVELOPMENT OF THE HUMAN FOETAL VITREOUS BODY

I Biochemical changes

BY

JENS FALBE HANSEN NIELS EHLERS AND JUDITH KAROSSA DEGN

Only few biochemical data are available on the development of the vitreous body *Balazs Laurent & Laurent* (1959) measured the concentrations of ascorbic acid hexosamine hexuronic acid ester sulfate protein nitrogen hydroxyproline and calcium in the developing cattle vitreous body from 2 month old embryos to 10 year old adult animals *Bembridge & Pirie* (1951) measured the total nitrogen and the hexosamine concentration in the rabbit vitreous humour during the first weeks after birth To the best of our knowledge similar biochemical analyses have not been carried out on the human foetal vitreous body

As an opportunity arose to examine fresh human foetal eyes we decided to perform as many relevant analyses as possible This proved however to be a difficult task owing to the very small size and the limited number of eye balls which was available For these reasons the accuracy of some of the results is not quite up to the standard we should have wanted but owing to the uniqueness of the material we decided to publish them along with the other more reliable results

Methods

Material

This comprises eyes from 22 human foetuses removed by caesarean section in connection with legal abortion and 1 foetus *delivered by* spontaneous abortion The eyes were excised and frozen at −20 C within 20 minutes post partum

Received May 16th 1968

This investigation was supported by a grant from Landsforeningen til Kræftens Bekæmpelse

Ophthalmoscopy both eyes Owing to the cataract it is only possible to catch a glimpse of lower part of the fundus through the coloboma of the iris Here a large coloboma of the retina and the choroid is seen Its extension upwards towards the optic disk cannot be followed

Discussion

Recently *Rubinstein* (1967) has summarized the findings in 31 patients with the Rubinstein Taybi syndrome The patient described in this paper has all the important features of the syndrome and some of the rarer ones as well Especially the ophthalmological findings are striking Apart from the commonly seen antimongoloid slant of the palpebral fissures and exotropia he has a typical bilateral coloboma of the iris the lens and the choroid He also *has cataract on both eyes Cataract was present in only 3 of the above men*tioned 31 cases and coloboma of the iris and the fundus in 2 cases Coloboma of the lens has not been described previously It is evident that the visual handicap of this patient is not the least serious of his multiple defects

Another interesting feature is the patient s age He is 62 years old whereas all the patients of *Rubinstein* are below the age of 16 years This seems to indicate that the condition is not incompatible with longevity

Summary

A case of the Rubinstein Taybi syndrome is described Apart from the usual facial and skeletal deformities this patient has bilateral cataract and bilateral typical coloboma of the iris lens and fundus

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Table 1

Composition of developing human vitreous body

Crown rump length	Number of eyes	Sialic acid µg/ml	Soluble protein mg/ml	Hexosamine µg/ml	Hexuronic acid µg/ml	Hydroxy proline µg/ml
60–80	2	164.0	7.0	–	–	–
80–100	2	–	20.4	–	–	17.8
100–120	5	163.0	12.1	112.4	–	19.3
120–140	1	129.0	9.6	–	–	–
	4	151.0	4.3	73.6	–	–
	2	152.0	6.5	–	–	–
140–160	2	144.0	9.0	121.2	–	7.4
160–180	1	137.0	10.4	–	–	24.2
	1	126.0	8.6	105.0	–	–
180–200	1	–	–	–	–	0.8
200–220	1	37.8	3.6	27.8	23.0	2.5
220–240	1	59.4	1.6	–	–	–
Adult vitreous body		15–20	1–1.5	20–40	20–40	10–20

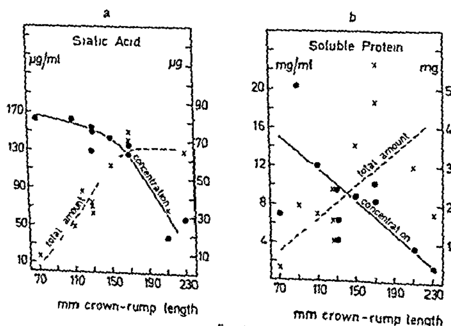


Fig. 1

Relation between crown rump length and concentration and total amount of sialic acid and soluble protein in the developing human vitreous body

Preparation

The anterior segment and the sclera choroid retina were carefully removed from the frozen vitreous body under a dissection microscope. The vitreous bodies of the various age groups were pooled and after thawing spun for 2 hours at 105 000 × g in a Beckman Spinco preparatory ultracentrifuge at 4° C. The supernatants were carefully decanted off and the sediment pellets were saved for hydroxyproline determination.

The centrifuged vitreous samples were dialyzed against destilled water for 2 hours at 37° C in a microdialysis apparatus (Kunz Copenhagen).

All analyses had to be done on much smaller volumes than described by the authors of the methods used. Control determinations on test solutions of various concentrations gave satisfactory results in spite of the reduction in volume. In most instances the samples were diluted with destilled water in order to obtain a sufficient amount to work with.

The spectrophotometric readings were performed on a Zeiss PMQ II spectrophotometer using semimicro quartz cells.

Analyses

Hexosamine. After hydrolysis with 8 N HCl for 8 hours at 95° C the hexosamine concentration was determined according to *Swann & Balazs* (1966).
Hexuronic acid was determined by the carbazole method of *Dische* (1947).
Protein determination was carried out according to the method of *Lowry et al.* (1951).
Sialic acid. After hydrolysis for 1 hour at 80° C with 0.1 N HCl the sialic acid content was determined by the thiobarbituric acid method of *Aminoff* (1961).
Hydroxyproline. After hydrolysis with 9.6 N HCl for 6 hours at 100° C in sealed glass tubes the hydroxyproline content was determined according to *Martin & Axelrod* (1953).

Results

The data are presented in Table I grouped according to the foetal crown rump length. Values for the adult vitreous taken from *Falbe Hansen* (1966) are included for comparison.

Fig. 1 is a diagrammatic representation of the results in relation to the crown rump length. The total amounts of sialic acid and soluble protein have been calculated from the weight of foetal eyes from the various age groups as given by *Ehlers et al.* (1968).

The results are in agreement with the assumption that an acidic glycoprotein is present in the developing vitreous The formation of this glycoprotein apparantly ceases at the time when the vitreous becomes avascular and the primary vitreous disappears

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Discussion

According to the curves in fig 1 the concentrations of both sialic acid and soluble protein show a fall during foetal life The total amount of sialic acid increases until a crown rump length of about 170 mm (20th menstrual week) The later values remain constant The total amount of protein seems to increase during the whole period of observation

The concentration of hexosamine is also highest in young embryos and slowly decreases with age The spectrophotometric readings in the hexuronic acid analysis were in *all* samples *but one too low to permit a calculation of the* concentration which accordingly must have been very low

Hydroxyproline determination was performed on the sediment pellets obtained after centrifugation of the vitreous samples These pellets were extremely small and an uncontrollable loss of material during the decantation cannot be ruled out This explains the unsystematic variation of the results It seems justifiable however, to regard the values as minimum values

There is a remarkably good qualitative agreement between our results and those given by *Balazs et al* (1959) for steer vitreous body Thus similar falls in the concentrations of soluble protein and hexosamine are encountered in foetal vitreous from humans and steers

The low concentration of hexuronic acid in the early stages of development is also in accordance with the findings on foetal steer vitreous This indicates that the synthesis of hyaluronic acid is a comparatively late phenomenon in the development of the vitreous body

The fall in sialic acid concentration is interesting The corresponding falls in the concentrations of soluble protein and hexosamine are compatible with the assumption that an acidic glycoprotein is present in the human foetal vitreous body The presence of such a glycoprotein in embryonic steer vitreous has been suggested by *Balazs et al* (1959) on the basis of electrophoretic experiments Another indication of the presence of a foetal glycoprotein in the vitreous is *that the total amount of sialic acid remains constant after* a certain stage of development This corresponds roughly to the time at which the hyaloid vessels obliterate and the vitreous becomes avascular

Summary

Biochemical analyses on the foetal human vitreous body at various stages of development showed a fall in the concentrations of soluble protein sialic acid and hexosamine during foetal life

The presence of hexuronic acid was only detectable at a late stage

around 3 5 mCi and the isodoselines applicable are illustrated in Fig 2 For a detailed description of the applicator see Rosengren and Tengroth (2)

Procedure

The silver ring is fixed to the limbus of the cornea with episcleral sutures (Fig 3) The arm on the ring is advanced through a conjunctival incision to the posterior part of the globe and then bent in order to press the ball against the sclera The impression of the ball into the sclera is seen with the ophthal moscope as a protrusion of the eye ground and the position can be checked so that the ball is placed exactly in relation to the tumor The retinoblastoma is then covering the applicator A suitable impression of the applicator can always be obtained by bending the arm in either direction Prior to the applica

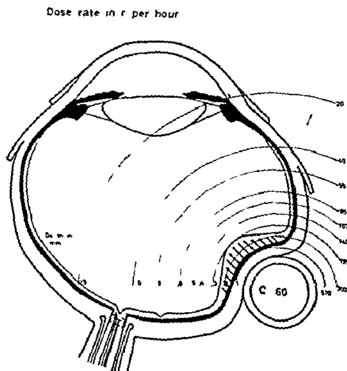


Fig 2
Acta Radiologica 1963 (Rosengren and Tengroth)

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THE TREATMENT OF RETINOBLASTOMAS WITH A ^{60}CO APPLICATION

BY

B TENGROTH AND B H O ROSENGREN

For more than six years a special ^{60}Co applicator has been used as a routine method for the treatment of patients with retinoblastoma This applicator which was described by Tengroth (1) and Rosengren and Tengroth (2) is a modification of that originally designed by Stallard (3) The device is in the form of a silver ring which can be sutured circumlimbal to the episclera Attached to this ring is a malleable arm the distal end of which is threaded to receive the platinum covered cobalt applicator The size of the ring as well as the length of the arm can be chosen to fit the individual case (Figs 1 a and 1 b)

The radioactivity which in 1960 measured about 10 mCi has decreased to

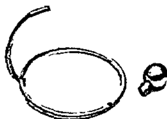


Fig 1 a



Fig 1 b

Acta Radiologica 1963 (Rosengren and Tengroth)

Received May 20th 1968

Table 1
Relative depth doses from the ^{60}Co eye applicator

	Depth (distance from the applicator)			
Depth	1 mm	2 mm	3 mm	4 mm
Dose	100 %	52 %	34 %	25 %

Up to the present time 10 cases of retinoblastoma and 4 malignant melanomas have been treated Only the former will be presented here

Case 1 A 12 month old girl with bilateral retinoblastomas Her left eye had been removed at another hospital and half a year later tumor masses were observed in the right eye On admission to this hospital the tumor masses covered an area of 6 optic disc diameters (O D D) and were treated with a series of photocoagulations and diathermy without success She was then treated with ^{60}Co applicator twice (September and October 1960) with estimated dosages of 10 000 rads and 6000 rads respectively Since then the patient has been seen several times each year In June 1967 her visual acuity was 5/30 and no sign of tumor recurrence She could manage to walk in a room without difficulty

Case 2 A boy age 3 with bilateral retinoblastomas The left eye was removed and in 1958 the tumor affecting more than half the retina in the right eye was treated with external X rays with a dosage estimated at 4900 R in combination with administration of triethylene melamine (TEM) In November 1960 new tumor masses were observed which disappeared after treatment with the ^{60}Co applicator up to 12 000 rads However six months later a new retinoblastoma was observed. This time the tumor was treated with the applicator with 6000 rads and after another seven weeks with



Case 1

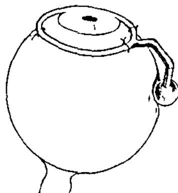


Fig 3
Acta Radiologica 1963 (Rosengren and Tengroth)

tion which is usually performed when the patient is examined for the first time *under general anesthesia a ring with a suitable diameter and arm length is* chosen then the cobalt ball is adapted to the ring and applied to the patient s eye After an appropriate length of time the applicator can be removed using local anesthesia

Our experience with this method during the past six years has been very encouraging since the operative procedure is very simple compared with earlier methods and the time required for the operation is short In addition the ability to position the applicator exactly corresponding to the tumor is con sidered to be advantageous

Dosage

The application time has been increased from 12 to 34 hours because of the decay in activity of the radiocobalt We have generally administered a single dose of 10 000 to 13 000 rads to a depth of 1 mm during the above mentioned times This dose appears to correspond to the 19 000 rads given by the Stallard applicator during 100 hours According to the depth dose values and isodose lines presented in Table I and Fig 2 for instance the retinal dosages are 12 000 rads at 1 mm depth 6300 rads at 2 mm 4100 rads at 3 mm and 3000 rads at 4 mm respectively

The good results presented by Stallard (4 5) using local ^{60}Co applications in cases of retinoblastoma are based on a large amount of data It seems there fore reasonable to assume that this kind of treatment is well documented The results with our modified method do not differ significantly from those ob tained by Stallard (4 5)

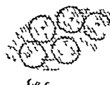
August 1967 the visual acuity was finger counting (+ 10 0) 30 cm. Secondary cataract but no tumor was observed

Case 6 A three month old boy with bilateral retinoblastomas whose mother and uncle had suffered from retinoblastomas The right eye was removed prior to his admission to this hospital A small 3 O D D tumor in the left eye was observed in June 1964 and treated with ^{60}Co 12 300 rads A new ? O D D tumor was observed and treated with 12 300 rads in August 1964 Since then the eye has been examined several times and in July 1967 there was no sign of a tumor in the fundus and the boy had good fixation Subjective visual testing was not reliable as he was too young for it

Case 7 A boy age five months On admission he had bilateral retinoblastomas The right eye was removed In the left eye great tumor masses were observed in the nasal and temporal portions of the fundus affecting more than half the retina Three different areas in the nasal portion were treated with 10 000 rads in October 1964 and in November the lateral portion was treated with three applications with a dosage of 10 000 rads each An elevation of the retina was observed one month later In December 1964 and January 1965 another three applications were carried out with equal dosages to the lateral field Ophthalmoscopic examination in August 1965 revealed *no trace of tumor masses* The retina was pigmented at the site where the tumor had been and the boy had no difficulty in fixation Later on in March 1967 he developed a cataract hemorrhages and phthisis bulbi and it was decided to removed the eye

Case 8 A three year old girl with bilateral retinoblastomas Her right eye was removed at the age of two months and eight months later a 2 O D D tumor was seen in the left eye The tumor was treated with one series of photocoagulations and conventional X ray therapy to an estimated dose of 3500 R Five months later another tumor was treated with a series of photocoagulations The tumors disappeared and the patients was free from symptoms for 15 months when a recurrence of the last treated tumor was observed The patient was then admitted to this hospital in March 1966 and a 1? O D D tumor was treated with the ^{60}Co applicator using two applications with 12 000 rads and with an estimated total dose of 15 000 rads at 1 mm depth On ophthalmoscopic examination one month later it was noted that the tumor was in regression This was also observed at subsequent monthly examinations six months





Case

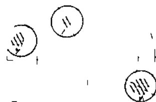
Case 6

7000 rads against a recurrence in the first treated area However new tumor masses appeared and therefore the right eye was removed

Case 3 A one year old boy with bilateral retinoblastomas On admission the right eye was filled with tumor masses and the left eye had two tumors each size of approximately 4 O D D The right eye was removed and each tumor in the left eye was treated with 12 500 rads in November and December 1961 A third tumor of approximately 3 O D D was found in January 1962 and treated with 12 500 rads Two months later the tumors had decreased in size An increased pigmentation and edema was seen in the retina surrounding the tumors By May 1965 the tumors had disappeared a slight pigmentation was observed and the visual acuity was 5/5 (refr ± 0) In May 1967 there was no change

Case 4 A boy age 2 with bilateral retinoblastomas On admission his right eye revealed diffuse growing tumor masses in the fundus and this eye was removed In the left eye a 9 O D D tumor was found and treated with ^{60}Co with 10 000 rads in January 1962 and again in May 1962 with 7000 rads Four months later it was apparent that the tumor had been replaced by an edematous tissue with varicose vessels and hemorrhages The changes were considered to be post radiological in origin In March 1963 visual acuity suddenly decreased and a vitreous hemorrhage was observed which probably emerged from one of the varicose veins No tumor was observed In August 1967 edema and white spots were noted in the treated region of the retina The visual acuity was now 5/20 and no hemorrhage or retinal detachment was observed

Case 5 A boy age 3 with bilateral retinoblastomas The right eye had been removed prior to the boy s admission to this hospital and the left eye had been treated with external X rays in March and April 1963 (6000 rads) for a large tumor in the lower lateral part of the fundus exceeding more than 1/3 of the retinal surface An edema of the tumor masses was observed but a month later a recurrence appeared The tumor covered an area in the fundus that made one application of the ^{60}Co ball insufficient Because of the X ray dosage already applied to this eye it was with great skepticism that treatment with the ^{60}Co applicator was started From the 18th to the 23rd of July 1963 five different applications with 13 700 rads were used on different parts of the tumor One month later the tumor masses had been replaced by edema and white spots in the retina Later on a cataract appeared which was removed in 1966 In



Case 3



Case 4

up to 15 000 rads in January 1967 At subsequent examinations the tumor was seen to be regressing At examination in September 1967 the tumor had been replaced by edema with no sign of recurrence The girl had no difficulty in fixation

Discussion

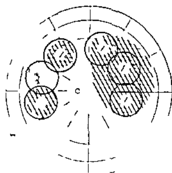
The patients had tumors which were managed in different ways In some of them (1 2 5 and 8) a previous treatment with external X ray combined with TEM and/or photocoagulation and diathermy had been used prior to the ^{60}Co application In these cases the alternative to ^{60}Co has been removal of the eye

In case 7 the tumor masses covered more than half the fundus and the cobalt application could be interpreted as a desperate try

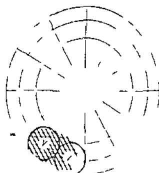
As has been pointed out by Stallard (6) and by Reese and Ellsworth (7) the size of the tumor influences the result of treatment The tumor size at first examination of our cases is given in Table II and also the vision after the treatment

Table II
Tumor size of first examination and visual results

Case	No of tumors	O D D	Tumor exceeding more than 1/4 of the retinal surface	Group according to Reese	Vision after treatment with ^{60}Co
1	1	6		II	5/30
2	1	~ 15	X	IV	eye excised
3	2	4		II	5/5
4	1	9		II	5/20
	1	~ 15	X	IV	perception of light
6	1	3		I	perception of light and projection
7	1	~ 15	X	IV	eye excised
8	1	2		I	5/15
9	2	~ 15	X	III	perception of light
10	1	2		I	perception of light and projection



Case 7

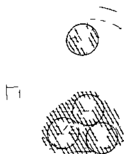


Case 8

later the tumor had disappeared Examined in August 1967 there was no sign of tumor and the visual acuity was 20/60

Case 9 A three year old girl with bilateral retinoblastomas The left eye was removed and tumor masses in the right eye were observed extending from the macula to the equator in the lower part of the eye and effecting about 1/4 of the retinal surface A small tumor was also observed in the upper part of the fundus After admission to this hospital in March 1966 the larger tumor area was treated with three ^{60}Co applications of 12 000 rads and the estimated total dose at 1 mm depth was 15 000 rads The small tumor was treated with one application of 13 000 rads At subsequent monthly examinations the tumors were in regression After six months calcium like deposits were seen in the tumor areas and there were no signs of tumor activity In March and September 1967 no tumor was seen but hemorrhages were observed

Case 10 A two year old girl with bilateral retinoblastomas The left eye was removed in December 1966 and in the right eye a small 2 O D D tumor was observed in the upper lateral part of the eye This tumor was treated with one ^{60}Co application



Case 9



Case 10

great advantage The applicator is also comparatively easy to handle Applications can be performed covering a larger area by employing successive treatment as in cases 5 and 7 where five and six applications respectively were made The applications were placed so that they covered the tumor area but when using the applicator like this our original intention of simple handling is more or less spoiled

Cases 3 4 6 and 10 were more favorable since they involved isolated tumors not previously treated with other methods We therefore still have the impression that the application is most suitable in cases with this type of tumor

In cases with more extended tumors but not exceeding 1/4 of the retinal surface Stallard s original applicators seem to us to be useful In tumors exceeding 1/4 of the retinal surface other methods are recommended external radiation with photons or high energy electrons (8) eventually combined with chemotherapy according to Reese

Summary

A ^{60}Co applicator for treatment of retinoblastoma is described Ten patients have been treated with the applicator since 1960 The treatment results are comparable with other methods in cases with comparable tumor volumes The applicator seems to be the most suitable in cases with solitary small tumors where its advantage of exact local positioning can be displayed In other types of cases the use of other methods is recommended

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In 77 patients where less than 1/4 of the retinal surface was affected Stallard reports success in 62 patients and in another group where the tumor exceeded more than 1/4 of the retinal surface the treatment was successful in only one of 20 patients As can be seen from Table II the tumor in 6 of our patients did not exceed more than 1/4 of the retinal surface and here all the patients have a useful vision This group of patients belongs to groups I and II according to Reese and Ellsworth (7)

In four of our patients the tumor exceeded more than 1/4 of the retinal surface and here two eyes were excised and two patients have only light perception These patients belong to Reese and Ellsworth s (7) groups III and IV

Our material does not permit a further subdivision into all Reese and Ellsworth s (7) groups but if groups I and II are taken together the tumor masses disappeared in 51 patients of 69 (74 per cent) and similarly in 24 of 40 cases (60 per cent) if groups III and IV are taken together

In our material no children have died from their retinoblastomas and the visual results are comparable with Stallard s and with Reese and Ellsworth s

Lens opacities have only been observed in two cases up to the present time However as demonstrated in fig 2 about 5 per cent of the radiation that is applied to the retinoblastoma will reach the lens if the tumor is situated in the posterior area of the fundus and hence the critical limit for cataract (500 rads) has been exceeded

When large tumor masses have been treated the reaction in the adjacent parts of the retina has been obvious A few weeks after the application an edema in the retina is found and sometimes this edema is difficult to differentiate from a detachment The tumor tissue is deteriorated and can be observed as white patches in the vitreous body After a few months white calcium like deposits are seen in the tumor area in combination with pigmentation of the retina and formation of telangiectases Hemorrhages have been observed in four cases 4 5 7 and 9 but the resorption has been relatively good in case 4 In case 5 in which external X ray treatment and five applications have been performed and in case 7 with six applications varicose vessels have been found and new hemorrhages can be expected with poor vision as a result In case 7 with six applications also a phthisis bulbae developed

The advantages of the Stallard method and the above described method using local ^{60}Co applicators over external radiation of the whole eye is that only the tumor affected area of the retina is irradiated and destroyed while the rest of the retina is more or less free from irradiation damages In Reese and Ellsworth s treatment method where external radiation was combined with chemotherapy the retina was remarkably unaffected by the radiation but on the other hand the side effects of chemotherapy have to be considered

Originally our method was designed for the treatment of isolated tumors where the precise positioning of the applicator behind the tumor would be of

great advantage The applicator is also comparatively easy to handle Applications can be performed covering a larger area by employing successive treatment as in cases 5 and 7 where five and six applications respectively were made The applications were placed so that they covered the tumor area but when using the applicator like this our original intention of simple handling is more or less spoiled

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GLAUCOMA MIOTIC THERAPY AND CATARACT

IV Chronic simple glaucoma and cataract formation *

BY

UNO AXELSSON

Introduction

The potent cholinesterase inhibitors now being used in the treatment of glaucoma viz echothiophate (Phospholine Iodide) paraoxon (Mintacol) di iso propyl fluorophosphate (Floropryl) and demecarium bromide (Tosmilen Humorsol) have been suspected of possessing cataractogenic properties (*Axelsson* and *Holmberg* 1966 *de Roetth Jr* 1966 a b *Shaffer* and *Hetherington Jr* 1966 *Tarkkanen* and *Karjalainen* 1966 *Axelsson* 1968 a b c) This suspicion has recently gained some support also from laboratory experiments (*Boles Carenini* and *Orzalesi* 1966 *Michon* and *Kinoshita* 1968) In a discussion of the findings reported in the first paper on this subject by *Axelsson* and *Holmberg* (1966) *Leopold* (1966) suggests that glaucomatous eyes may tend to cataract formation because they are disordered The concept that glaucoma eyes may have a tendency to lens opacification has occasionally been advanced by several authors Thus e g *Wheeler* (1933) writes That opacities of the lens develop rather frequently in glaucomatous eyes is known by all close observers of large experience *von Fieandt* (1949) states that cataract formation following cyclo dialysis is difficult to evaluate as slight opacification occurs in the lens even

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before operation and every glaucomatous eye obviously has a tendency to lenticular opacity"

In some cases, cataract may be a direct result of glaucoma But do all types of glaucomatous eyes tend to cataract formation? And, if so can this explain the high incidence of cataract in eyes with chronic simple glaucoma being treated with potent cholinesterase inhibitors?

The present work has been undertaken in an attempt to shed some light on these problems The first section of the paper will present a review of the literature on the relationship between cataract and glaucoma notably chronic simple glaucoma and the second section will give an account of a study of patients with this type of glaucoma

Review of the Literature

According to *Elschnig* (1922) cataract and glaucoma may both be present in an eye at the same time in the following alternatives

1 Cataract and glaucoma may be present independently of one another
2 The glaucoma may have been caused by the cataract
3 The cataract may be the result of the glaucoma

As far as the first alternative is concerned both cataract and glaucoma are more common in older age groups and the age factor as such should thus be sufficient to account for their simultaneous occurrence But has the glaucoma an accelerating effect on the senile cataract? This will be discussed below

Under the second alternative Elschnig mentions that glaucoma may develop (a) as a result of traumatic cataract, (b) as a result of displacement of the lens and (c) as a result of intumescent or hypermature cataract All these conditions are well known entities of no particular interest in the present context and require no further comments

To the third alternative Elschnig refers only cataracta glaucomatosa which according to him does not occur until in the degenerative stage of absolute glaucoma In later years also another type of cataract caused by glaucoma the so called cataracta disseminata subepithelialis glaucomatosa acuta seen after attacks of acute glaucoma has been described first by *Vogt* (1930) and after him also by many other authors To the third alternative may also be referred cataracts caused by treatment surgical or medical

Before discussing the relationship between chronic simple glaucoma and cataract it may be pertinent to give a brief summary of what is known about the different conditions included under the third alternative

Cataracta glaucomatosa That cataracts occur in the degenerative stage of absolute glaucoma is well known but opinions differ as to the characteristic features of this type of cataract One of the first descriptions was given by *Priestley Smith* (1879) who states that in its initial stage this cataract most frequently resembles a nuclear cataract but as time goes on the whole lens becomes extremely opacified and has then "a characteristic white or yellowish appearance such as occurs in the secondary cataract associated with disease in the ciliary region *Schmidt Rimpler* (1908) notes that as a rule cataracta glaucomatosa presents the picture of a common senile cataract with a hard nucleus and soft cortex but that it may sometimes resemble the opacification seen after iridocyclitis choroiditis and retinal detachment According to *Fuchs* (1910) it is important to differentiate between cataracta glaucomatosa – which is seen in the course of glaucomatous degeneration – and cataracta in oculo glaucomatoso a term which he applies to the cataract only occasionally seen in glaucoma simplex the former is characterized by the marked intumescence the bluish white colour and the bright silky lustre of the anterior surface whereas the latter presents a picture corresponding to its origin and nature *Vogt* (1931) is of the opinion that cataracta glaucomatosa does not in any way differ from the common types of complicated cataract Even the histological descriptions vary Thus e g *Samuels* (1947) considered the absence of folds in the capsule and the presence of subcapsularly located vacuoles to be typical of the cataract caused by glaucoma whereas *Redslob* (1955) did not find any characteristic lens changes in enucleated eyes with primary glaucoma

The main cause of cataracta glaucomatosa is considered to be a decrease in the production of aqueous due to degeneration of the ciliary body Deleterious products from the degenerative changes within the eyeball may also play a role (*Bellows* 1944)

Cataracta disseminata subepithelialis glaucomatosa acuta (Glaukomflecken) This condition is characterized by tiny white spots of irregular shape of a diameter of 0 02 to 0 3 mm arranged in rows beneath the anterior capsule often along the suture lines Gradually a certain regression occurs and as new lens fibres are being formed the spots are pushed deeper into the cortex As a rule the visual acuity is not impaired *Seidenari* (1940) meant that he had seen similar spots also in the posterior cortex but other authors e g *Vogt* (1931) *Auricchio* (1953) and *Lowe* (1965) deny the existence of such posterior lesions The genesis of these lens opacities is not certain It is noteworthy that they do not occur after all attacks of acute glaucoma For his part Vogt was of the opinion that the process does not only consist of a breakdown of lens fibres but may also be an exudative phenomenon *Sugar* (1957) considers the spots to be a result of the high intraocular pressure A support for this view is that similar spots have been observed also after severe contusion to the eyeball which

induces a pronounced, although shortlasting rise in intraocular pressure (*Vogt* 1931 *Sommer* 1940 *Auricchio* 1953) On the other hand there seems to be no correlation between the occurrence of Glaukomflecken and the severity and duration of the acute glaucomatous attack (*Nemetz* 1949 *Auricchio* 1953) Nemetz points out that similar changes also may occur e g after ammonia injury cauterization with 20 % zinc sulphate and penetrating injuries and suggests that these changes may be due to liberation of histamine or histamine like substances

It has also been proposed that common senile cataracts may be induced or accelerated by acute glaucomatous attacks (*Becker* and *Shaffer* 1965 *Lowe* 1965) but no statistical study seems to have been presented in support of this view

Cataract following glaucoma surgery That cataracts may develop both as an early and late complication of glaucoma surgery is well known These complications seem to occur only if the chamber has been opened (*Morano* 1946) Both early and late postoperative cataracts may be the result of injuries caused by instruments (*Leopold* 1960) The genesis of the cataract in cases in which such injuries can be ruled out has been discussed fairly extensively That maintained postoperative hypotony after fistulizing surgery plays a role was pointed out as early as in 1914 by *Meller* and later also by a large number of other authors among them *Leopold* (1960) who suggests that "the altered physiologic character of the eye is the main factor *Leydhecker* (1966) and *Cristiansson* (1967) on the other hand do not regard postoperative hypotony as a decisive factor *Magni* (1950) blames the preoperative treatment in many eyes miotics give rise to posterior synechiae which may be broken during the operation and thus capsular lesions may occur Another cause may be displacement of the lens due to the formation of synechiae (*Legrand* 1954 *Hobbs* and *Smith* 1954) That postoperative infection may be the cause of the cataract has been pointed out e g by *Fanta* (1948) who also states "Bei unseren Fallen kann die glaukomatose Schadigung als Ursache der Starbildung ausgeschlossen werden da wir ja ein derart haufiges Auftreten einer Starbildung durch glaukomatose Schadigung gar nicht kennen und diese bei Glaucoma simplex meist nicht beobachten können"

Direct complications or sequelae of the operation have thus been held responsible for the high incidence of cataract observed after glaucoma surgery The condition of the eye at the time of the operation has received far less attention but has been thoroughly discussed by *Leydhecker* (1966) who emphasizes that the condition of the lens and above all the age of the patient seem to be factors of decisive importance for the final outcome it seems as though the lenses of younger people should better tolerate glaucoma surgery than do those of elderly persons

That the glaucoma disease as such may play a role in the development of postoperative cataract has been briefly discussed in a few papers but most authors have not paid any attention to this factor and no work seems to have been published demonstrating that the frequency of postoperative cataract should be higher the more advanced the glaucoma

Cataract following miotic treatment As mentioned above a considerable amount of evidence has accumulated showing that potent cholinesterase inhibitors may possess cataractogenic properties But no statistical investigation seems to have been published indicating that weaker miotics should have a similar action However laboratory experiments have demonstrated that pilocarpine may disturb the metabolism of the lens in different animal species (*Muller et al* 1956 *Hockwin et al* 1966 *Boles Carenini* and *Or alesi* 1966) and *Muller et al* (1956) described anterior cortical cataract formation in a patient treated exclusively with pilocarpine

It is obvious that valid conclusions as to the relationship between glaucoma and cataract can hardly be drawn from clinical studies of patients who have previously been treated either by surgery or by the administration of miotics

The concept of chronic simple glaucoma as predisposing to cataract formation may derive its origin from the fact that cataract is common in eyes in the degenerative stage of absolute glaucoma Thus *Gradle* (1936) writes Lens opacities may or may not be present in the early stages of compensated glaucoma and are entirely independent of the disease But the continued hypertension of an untreated compensated glaucoma leads eventually to disturbance of the osmotic function of the capsular epithelium and gradually increasing lens opacities which are very slow in becoming complete Similar views have been expressed by *Salus* (1920) Es ist ferner zu berucksichtigen dass Augen mit vorgeschrittenerem Glaukom an sich zu Auftreten von Katarakt disponiert sind wie schon das Beispiel der Cataracta glaucomatosa bei absolutem Glaukom beweist The elevated intraocular pressure is obviously thought to cause a gradual opacification of the lens toward the dense cataract in absolute glaucoma But is cataract considered as a characteristic feature in the clinical picture of chronic simple glaucoma? And if so what is the biomicroscopic picture of this cataract? Is it a specific type of cataract or is it a type of common senile cataract accelerated by the raised intraocular pressure?

An excellent review of the literature on glaucoma and its different manifestations from the 19th century and up to the first years of the 20th century has been published by *Schmidt Rimpler* (1908) His reference list comprises no less than 1646 papers and in addition, 19 textbooks! At that time gonioscopy had not yet been introduced and the classification of the various types of primary glaucoma was based on the presence or absence of inflammatory

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the glaucomatous cataract starts with a haziness of the nuclear or paranuclear portions rather than with distinct striae or patches of opacity in the peripheral parts

According to *Alajmo* (1925) the transparency of the lens is more or less impaired even in incipient cases of glaucoma simplex and even though no changes are to be seen on transillumination with the ophthalmoscope Characteristic slitlamp findings in all types of glaucoma should be (1) the presence of tiny flake like opacities of intense white colour in the posterior cortex or on the inner surface of the posterior lens capsule and (2) the intense multi coloured reflex of the posterior surface as in cataracta complicata Alajmo based his theory on a biomicroscopic study of 19 patients only five of whom were considered to have glaucoma simplex

On the basis of slitlamp examinations of eight patients two of whom had acute glaucoma and six glaucoma simplex *Seidenari* (1940) shows that there are two different types of cataracta glaucomatosa One of them the less common type is that described by *Vogt* (1930) as occurring after acute glaucomatous attacks whereas the second more common type is seen in cases of chronic glaucoma and is characterized by a silky reflex of the anterior lens capsule and a milky appearance of the lens substance It is this type of cataract that has a rapid progression after glaucoma surgery

Also *Duke Elder* (1940) is of the opinion that long continued pressure may give rise to cataract starting at first as a general haze especially posteriorly and eventually progressing to form a complicated cataract In persons with common senile cataract the advent of hypertension undoubtedly accelerates the development of cataract However Duke Elder does not present any statistical data or references

Morano (1946) is of the opinion that in all types of primary glaucoma a specific cataract can be observed which he calls cataracta glaucomatosa and which has the appearance of a cataracta complicata posterior with the following characteristics 1) the anterior cortex clear or slightly milky 2) the nucleus with increased optic density and 3) cloudy opacification of the posterior cortex small amber coloured opacities in the posterior pole and a yellowish reflex from the posterior lens Morano considers this to be the type of cataract that progresses after surgical procedures if the chamber has been opened He mentions that he has based his concept on a study of a large case material but only 14 cases are reported in his paper three of which were considered to have glaucoma simplex in one or both eyes and three glaucoma simplex in one eye and absolute glaucoma in the fellow eye In the three latter cases this specific type of cataract was seen in both eyes but was always more pronounced in the blind eye

An excellent review of the literature on the relationship between glaucoma and cataract was published in 1953 by *Auricchio* who also presents a case

symptoms Thus we must presume that the primary open angle glaucoma of to day corresponds to what was then termed glaucoma simplex Besides, there were at that time no reliable methods of measuring the intraocular tension and hence as a rule only advanced cases of glaucoma simplex were diagnosed In his description of the clinical picture of glaucoma simplex Schmidt Rimpler does not mention cataract Not even such eminent ophthalmologists as Elschnig and Fuchs (cf above) consider cataract as a characteristic feature in glaucoma simplex

It should of course also be remembered that at that time the slitlamp had not yet been introduced and the minutely detailed studies of the lens that are possible to day could thus not be performed then But nevertheless the lens was the subject of extensive studies above all by *Priestley Smith* (1879 1891) He was of the opinion that the rise in intraocular pressure seen in glaucoma simplex was the result of an increase of the sagittal diameter of the lens On the other hand cataractous lenses should be smaller than healthy ones and *provide some immunity against primary glaucoma unless a* pronounced degeneration of zonulae zinnii had occurred in which case there is an increased tendency to forward displacement of the lens and consequently to impairment *of the outflow Priestley Smith does not mention cataract* as a characteristic symptom in glaucoma but he points out that the lens of a glaucomatous eye often appears to be cataractous even though no opacities are present The *inexperienced observer may well be astonished to find that he can view with* the ophthalmoscope the minutest details of the fundus through a crystalline lens, which to the naked eye looks like a cataract almost ready for extraction *No explanation is given for this phenomenon*

Elliot (1922) is of the opinion that cataract may occur as a result of glaucoma The form of cataract secondary to glaucoma is characterized by the want of *definitions in its appearance It looks more like a smoky greenish or* bluish haze than like one of the ordinary forms of cataracts" The author does how *ever not give a more detailed description of or explanation for this* cataract *secondary to glaucoma nor does he report any case material of his own*

Also *Wheeler* (1923 cf Introduction) is of the opinion that glaucomatous eyes may tend to cataract formation the main cause of which should be inter *ference with the normal secretion and circulation of the aqueous As* in the common senile cataract the first changes are seen around the equator where the cortical fibres are youngest and thus most vulnerable and along the suture lines *The old notion of glaucomatous cataract was that it was* characteris tically greenish in colour but this was largely due to a curious deception Vogt in his slitlamp corneal microscope studies has not discovered any charac *teristics peculiar to glaucoma cataract" Also Wheeler does not present* any case material of his own

In a discussion of Wheelers paper *Wilder* (1923) says that in his opinion

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An excellent review of the literature on the relationship between glaucoma and cataract was published in 1953 by *Auricchio* who also presents a case

material of his own Out of 70 iridectomized patients with unilateral irritative glaucoma 12 patients had nuclear or nucleo-cortical cataract of a more or less progressive type in the operated eye. In ten cases the fellow eye apparently with no glaucoma displayed similar although less pronounced changes In 50 patients with unilateral glaucoma simplex, treated with miotics or operated on by means of cyclodialysis the same changes were observed in 11 cases in the treated eye and in 9 cases in the same or a lower degree in the eye with no glaucoma From these observations Auricchio draws the conclusion that the cataract usually seen in glaucoma is of common senile types but may be ac *celerated by the glaucoma or by surgery, the true glaucomatous cataract does* not appear until in a later stage when vision has been lost or is seriously reduced and its pathogenesis is to be sought in degenerative changes involving all tissues of the eye

The concept of chronic simple glaucoma as predisposing to cataract formation may derive its origin from theories concerning the relationship between pseudo exfoliation of the lens capsule glaucoma and cataract It is fully evidenced that the incidence of glaucoma is high in eyes with pseudo exfoliation Many authors *e g Gradle* and *Sugar* (1940) are of the opinion that eyes with pseudo exfoliation should also tend to cataract formation However a high incidence of cataract in eyes with pseudo exfoliation and a high incidence of pseudo-exfoliation in eyes with cataract need not necessarily imply that there is a direct relationship between the two conditions since both occur preferably in older *age groups (Bellows 1944) Tarkkanen (1962) did not find* any difference in cataract formation between the two eyes of non glaucomatous patients with unilateral pseudo exfoliation Nor were any such differences observed by *Klouman* (1967) in a similar investigation In a follow up of patients with unilateral pseudo exfoliation the latter author found a few cases in which the cataract gradually became more pronounced in the eye with pseudo exfolia tion from this he draws the conclusion that "the association of pseudo exfolia tion with cataract seems to be very slight but may be more pronounced after many years duration" Hence it does not seem to be fully evidenced that pseudo exfoliation should favour cataract formation nor that a simultaneous *occurrence of pseudo exfoliation and glaucoma should have such an effect*

It is obvious that opinions differ as to whether or not open angle glaucoma may predispose to cataract formation Some authors deny that this should be the case Most well known handbooks state that cataract secondary to glaucoma occurs only in the degenerative stage of absolute glaucoma and after attacks of acute glaucoma But some authors seem to be of the opinion that a specific type of cataract may be seen in eyes with chronic simple glaucoma These authors represent two different categories one group which apparently reports only their personal clinical impressions and does not present any case material

of their own and a second group which presents results from own investigations as a rule comprising only small series of patients Some of these authors refer to studies of groups of previously treated patients from which as has been pointed out above valid conclusions can hardly be drawn Besides different authors give different descriptions of this specific cataract a fact hardly calculated to strengthen the theories proposed The only investigation published which comprises a fairly large patient population is that reported by *Auricchio* (1953) He arrived at the conclusion that the cataract usually found in eyes with chronic simple glaucoma is of common senile types and that the glaucoma should have accelerated its progression But also Auricchio s investigation refers to previously treated patients and the results presented by him can thus hardly be taken as evidence in support of the concept that chronic simple glaucoma should accelerate the senile cataract

In this context an idea proposed by *Gjessing* (1967) appears to be of some interest *vi* that there may be some kind of antagonism between glaucoma simplex and cataract to the effect that the glaucoma may counteract the cataract formation Gjessing mentions that according to personal communications to him (1967) similar concepts should have been advanced by *Svartshoel* and *Traquair* but no study seems to have been published concerning a possible antagonism of that kind

Current Investigation

As appears from the review of the literature presented above no reliable statistical investigation seems to have been published in support of the concept that chronic simple glaucoma should predispose to or precipitate cataract formation Cataractous changes clearly attributable to the glaucoma do not develop until in the degenerative stage of absolute glaucoma However some authors seem to be of the opinion that a longstanding ocular hypertension may gradually damage not only the optic nerve but also the lens

To get some insight into these problems the ideal approach would no doubt be to induce a unilateral constant intraocular pressure elevation in a number of subjects with healthy eyes without causing any damage *to the eyes and then* keep them under observation for a number of years but this is of course out of the question Nor has it been possible to find an experimental animal in which a sustained pressure elevation could be achieved for some length of time

The only practical method is thus to study individuals who already have an elevated intraocular pressure Although from a genetic point of view primary open angle glaucoma is considered to be a bilateral disease it is as a rule present in only one of the eyes or in different stages in the two eyes when

the diagnosis is first established A study of a number of such patients may yield some information as to whether an abnormal intraocular pressure does in fact also damage the lens

Material and Methods

The purpose of the present investigation was to select among the glaucoma population of the eye clinic of Sabbatsberg Hospital Stockholm a number of patients with unilateral or "asymmetrical" chronic simple glaucoma in order to ascertain if these patients when first seen at the clinic also displayed any differences in the state of the lenses in the two eyes

The patients admitted to the eye clinic for investigation and treatment of glaucoma are in part derived from the out-patient department of the clinic and in part referred from private ophthalmologists The routine examinations comprise the following schedule all particular items of which are carried out in all cases unless the general condition of the patient makes it impossible

1 Determination of refraction and visual acuity according to the method of Donders by means of the Monoyer or Monoyer Granström visual charts
2 Examination of the eye fundus by direct and indirect ophthalmoscopy
3 Slitlamp examination of the anterior segment of the eye and the lens
4 Gonioscopy
5 Visual field tests by means of the Goldmann perimeter and the Bjerrum screen
6 Applanation tonometry and tonography in most cases performed in combination with the water-drinking test
7 Diurnal measurements of the intraocular pressure by means of the standard Schiotz tonometer (1955 scale)

From 1965 inclusive the lenses of all patients with open angles have been examined after dilation of the pupil Since the schedule delineated above was introduced at the clinic in 1960 reliable data are available in the records from that year on and it has thus also been possible to perform a retrospective study of patients examined in the years 1960–1964 Prior to 1965 however examinations of the lens and eye fundus under mydriasis were performed only in cases not permitting a close study of the fundus through the undilated pupil

In the clinic the various types of primary glaucoma are classified on the basis of the gonioscopic findings The angle of the anterior chamber is graded according to the system introduced by *Shaffer* and *Schwartz* (1957) cases with angles of types 3 or 4 are classified as glaucoma simplex This diagnosis is

applied also to eyes in which the only sign of glaucoma is ocular hypertension Cases with total loss of function are diagnosed as glaucoma absolutum Cases with pseudo exfoliation are classified as primary glaucomas the diagnosis glaucoma capsulare is not used

When studying the records of a number of patients with the diagnosis glaucoma simplex it was however evident that in the majority of cases the extent of the glaucoma differed more or less in the two eyes It was also found that the value taken as the upper limit for normal tension had undergone certain changes in the course of the years For the selection of the material it thus proved to be necessary to establish diagnostic criteria for ocular hyper tension and asymmetrical glaucoma

Ocular hypertension As is well known it is difficult to establish a normal intraocular tension for a particular eye Hence abnormal or elevated intra ocular tension is generally expressed in statistical terms based on findings in the normal population Measurements with the applanation tonometer (sitting position) have given a mean value of 15 4 ($\delta \pm 2$ 5) mm Hg*) and measurements with the Schiotz tonometer 16 1 ($\delta \pm 2$ 8) mm Hg (cf *Becker* and *Shaffer* 1965) Mean plus 2 δ is regarded as the upper limit for normal tension and mean plus more than 3 δ as abnormal Values between 2 and 3 δ from the mean are con sidered as suspect elevated tension Since different methods of measurement yield different values simplifications are generally used for practical purposes $\leq$ 21 mm Hg being regarded as normal intraocular pressure 22–24 mm Hg as suspect elevated pressure and $\geq$ 25 mm Hg as abnormal pressure (ocular hypertension) According to *Goldmann* (1960) this latter value indicates the presence of glaucoma

These intraocular pressure values have also been applied in the present investigation The evaluations of the tension have in the first place be n based on measurements with applanation tonometers only in cases in which repeated applanation values were not available have they been based on measurements with Schiotz tonometers

Asymmetrical glaucoma On the basis of the intraocular pressure limits indicated above as well as the state of the optic disc and of the visual field criteria were established (see Table I) by which each particular eye could be referred to one of the six different stages of chronic simple glaucoma thus listed In terms of this classification each case of chronic simple glaucoma could be graded numerically according to the stage of glaucoma deemed to be present in either eye e g 2–0 2–1 2–2 etc Since as mentioned above chronic simple glaucoma is regarded as a genetically bilateral disease it has been

*) δ is the standard deviation

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*) δ is the standard deviation

Table I

Criteria used for classification of eyes into different stages of chronic simple glaucoma

Stage of glaucoma	Criteria
0	Tension in repeated examinations not exceeding 21 mm Hg on more than one occasion Disc and field normal
1	Tension on at least two separate occasions 22 mm Hg or more but not 25 mm Hg or more Disc and field normal
2	Tension on at least two separate occasions 25 mm Hg or more Disc and field normal
3	*Tension on at least two separate occasions* 25 mm Hg or more Disc glaucomatous Field normal
4	Tension on at least two separate occasions 25 mm Hg or more Disc glaucomatous Field with early glaucomatous defect i e enlargement of the blind spot up to a large Bjerrum scotoma
5	Tension on at least two separate occasions 25 mm Hg or more Disc glaucomatous Field with a large quadrant or even more extensive defect

considered justifiable when glaucoma was present in one eye to grade the fellow eye as being of stage 0 or 1

The glaucoma has been deemed to be asymmetrical if the difference between the two eyes amounted to two stages or more In this way the patients could be divided into ten different subgroups of asymmetrical glaucoma (see Tables III and IV) The eye exhibiting the more advanced stage of glaucoma by the criteria thus established has been taken to represent the eye under study and has been termed *the glaucoma eye* the contralateral eye with less advanced glaucoma or no signs of the disease has been termed *the reference eye*

Selection of the material By means of the ledger in which are entered all patients hospitalized at the clinic and the diagnosis made in each case it was possible to single out all records relating to patients who had been admitted to the clinic under the diagnosis of glaucoma simplex in one or both eyes during the period from January 1st 1960 up to July 31st 1967 when this investigation was terminated and to list all patients who when first seen at the clinic had asymmetrical glaucoma by the criteria presented above In the list were not included patients who had undergone surgery of any kind in either eye or patients with a history or signs of trauma or inflammatory disease of the inner eye unilaterally or bilaterally or cases of glaucoma simplex in one eye and glaucoma absolutum in the other In all records representing about 1250 patients were gone through and 407 were listed In addition three patients were found with respect to whom a classification of the glaucoma according to Table I could not be made due to lens opacities in one of the eyes these three cases will be presented in detail below Finally out of the initial list of 407 patients 211 had been treated with miotics for shorter or longer periods prior to their first visit to the clinic and were thus excluded since – as mentioned in the first section of this paper – valid conclusions as to the possible correlation between glaucoma and cataract can hardly be drawn from previously treated cases Of the remaining 196 patients two had to be disqualified due to incomplete data on the state of the lenses these two cases will also be reported separately below After these eliminations there remained for the final evaluation a group of 194 patients of whom 47 had been examined under mydriasis for the purpose of this study and 147 had been evaluated on the basis of data available in the records In the following the former group will be referred to as *examined cases* and the latter group as *retrospective cases* Since however many of the patients in the latter group are still attending the clinic for regular checks it has been possible in several cases to verify the initial evaluation by a re examination performed by the author

Evaluation of the lens In clinical work a lens is deemed to be clear if no opacities are found in that part of the lens which is accessible to inspection and to be cataractous if opacities are present By these criteria alone each patient could be classified into one of the following four categories *vi* clear lenses bilaterally bilateral cataract *cataract only in the glaucoma eye and cataract* only in the reference eye

Particular attention has also been paid to the patients with bilateral cataract in order to ascertain if the cataractous process was more advanced in the glaucoma eye As is well known there is no reliable clinical method by which the degree and extent of opacification in a lens can be measured As a rule it is related to the visual impairment induced by it but this method of evaluation is fairly unsatisfactory since e g a small posterior polar cataract may

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Table II

Criteria used for classification of patients with bilateral cataract.

Symbols	Criteria
+	Cataract more advanced in the glaucoma eye visual acuity of the two eyes differed or should have differed by ?/10 or more
+?	Cataract more advanced in the glaucoma eye visual acuity of the two eyes differed or should have differed by less than 2/10
0	No appreciable difference with respect to the cataractous process in the two eyes
?	Cataract more advanced in the reference eye visual acuity of the two eyes differed or should have differed by less than 2/10
-	Cataract more advanced in the reference eye visual acuity of the two eyes differed or should have differed by 2/10 or more

patients were deemed to have unilateral cataract 2 of them had cataractous changes in the glaucoma eye and 3 in the reference eye

° In the examined group 22 patients (47 %) had clear lenses bilaterally and 23 patients (49 %) had bilateral cataract The remaining two patients had cataract only in the glaucoma eye

To Table IV the following comments may be made

I In the retrospective as well as in the examined group no essential differences with regard to the cataractous process in the two eyes were found or were judged to be present in about two thirds of the patients The distribution of patients rated as plus or minus is about even in both groups as is also the distribution of cases rated as plus? or minus?

° In the examined group the classification of the 23 patients did not meet with any difficulties In the majority of the cases in which the visual loss was judged to be due exclusively to cataract there seemed to be good correlation between the decrease in visual acuity and the degree of opacification present In the retrospective group of 61 patients on the other hand the classification

cause a larger decrease in visual acuity than a widespread cuniform cataract besides a visual loss due to other causes than cataract may render the evaluation more difficult Since, however, this method had previously been employed in the retrospective cases it has been applied also in the present study A difference in visual acuity between the two eyes of 2/10 or more fully explained by the state of the lenses has been taken as a criterion of asymmetry For cases with reduced visual acuity attributable also to other causes asymmetry has been deemed to be present if it was found at the examination or was evident from the records that the degree and extent of the lens opacification differed considerably in the two eyes

In presenting the results the following symbols have been used for the different categories of patients with bilateral cataract *vi* plus (+) as denoting patients in whom by the criteria thus established the cataract was more advanced in the glaucoma eye minus (–) as denoting patients in whom the process was more advanced in the reference eye nought (0) as denoting patients with no appreciable difference with respect to the cataractous process in the two eyes plus? (+?) and minus? (–?) respectively, as denoting patients in whom a higher degree of opacification was present, or was deemed to be present in one of the eyes but in whom the two eyes differed by less than 2/10 or in whom no definite evaluation of the difference was possible

The criteria employed for this classification of the different cases of bilateral cataract are listed in Table II

Results

As appears from the foregoing the patient population under study has been divided into ten subgroups according to the different types of asymmetrical glaucoma present in each case In Table III the material has been listed in subgroups on the basis of the state of the lenses (clear or cataractous) In Table IV the classification has been based on the criteria presented in Table II for the patients with bilateral cataract In both tables the ten subgroups have been arranged from the top downwards in a numerically rising degree of asymmetry of the glaucoma and the retrospective and the examined cases have been listed separately

To Table III the following comments may be made

I In the retrospective group 81 patients (55 %) were deemed to have clear lenses bilaterally and 61 patients (42 %) to have bilateral cataract Only 5

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Table II

Classification, according to the criteria given in Table II of the patients with bilateral cataract divided into subgroups with respect to the different types of asymmetrical glaucoma present

Stage of glaucoma 1) 2)	Retrospective cases						Examined cases					
	Total number of patients	Classification according to criteria given in Table II					Total number of patients	Classification according to criteria given in Table II				
		+ No pats	+? No pats	0 No pats	−? No pats	− No pats		+ No pats	+? No pats	0 No pats	−? No pats	− No pats
−0	16	2	1	10	1	0	3	0	0	3	0	0
3−1	7	0	1	0	0	1	1	0	0	1	0	0
4−2	3	0	0	3	0	0	0	0	0	0	0	0
3−3	8	0	1	7	0	0	1	0	0	0	0	1
3−0	8	1	1	5	0	1	4	0	1	2	1	0
4−1	5	0	0	3	0	0	1	0	0	1	0	0
5−2	4	0	0	3	1	0	3	1	0	2	0	0
4−0	0	0	0	0	0	0	1	0	0	1	0	0
5−1	3	0	1	1	1	0	2	0	0	2	0	0
5−0	14	1	1	10	2	0	7	0	1	5	0	1
Total	61	4	6	42	5	4	23	1	2	17	1	2

1) glaucoma eye
2) reference eye

Table III

Classification according to the state of the lenses (clear or cataractous) of the patient population under study divided into subgroups with respect to the different types of asymmetrical glaucoma present

Stage of glaucoma 1) 2)	Retrospective cases: Total number of patients	Retrospective cases: Clear lenses bilaterally No pats	Retrospective cases: Bilateral cataract No pats	Retrospective cases: Cataract only in glaucoma eye No pats	Retrospective cases: Cataract only in reference eye No pats	Examined cases: Total number of patients	Examined cases: Clear lenses bilaterally No pats	Examined cases: Bilateral cataract No pats	Examined cases: Cataract only in glaucoma eye No pats	Examined cases: Cataract only in reference eye No pats
2 – 0	37	21	16	0	0	9	5	3	1	0
3 – 1	6	3	2	1	0	3	2	1	0	0
4 – 2	4	1	3	0	0	1	1	0	0	0
5 – 3	16	7	8	0	1	2	1	1	0	0
3 – 0	20	11	8	0	1	9	4	4	1	0
4 – 1	3	0	3	0	0	2	1	1	0	0
5 – 2	14	10	4	0	0	5	2	3	0	0
4 – 0	5	5	0	0	0	2	1	1	0	0
5 – 1	12	9	3	0	0	3	1	2	0	0
5 – 0	30	14	14	1	1	11	4	7	0	0
Total	147	81	61	2	3	47	22	23	2	0

1) glaucoma eye
2) reference eye

eye One patient had unilateral cataract in the glaucoma eye The investigation has thus not provided any convincing evidence in support of the concept that glaucoma when associated with pseudo exfoliation should predispose to cataract formation

3 As mentioned above two patients were excluded due to incomplete data on the state of the lenses One of them had asymmetrical glaucoma of the type 5–3 and one of the type 5–0 Since however the visibility of the eye fundus through the undilated pupil was good in both cases the state of the lenses was not likely to have been very different in the two eyes in any of these cases

4 As also mentioned above a classification of the glaucoma according to Table I could not be made in the case of three patients due to pronounced lens opacification in one eye These cases will be presented in detail below

Case 1 H H ♂ aged [illegible]8 years *O D* V A = c f 1–2 m Almost dense cataract Disc never seen State of field difficult to evaluate due to cataract Tension never exceeding [illegible] mm Hg – *O S* V A = 0 9 Cataract Disc glaucomatous Field on routine examination normal Tension 26–3[illegible] mm Hg Only O S treated

Comment Cataract more pronounced in the eye in which the presence of glaucoma could not be ascertained

Case 2 L F ♂ aged 73 years *O D* V A = 1 0 Incipient cataract, Disc and field normal Tension [illegible]0–[illegible]3 mm Hg – *O S* V A = c f 0 5 m Almost dense cataract Pseudo exfoliation Disc never seen Uncharacteristic field defect Tension 23–32 mm Hg

Comment Cataract more pronounced in the eye with ocular hypertension

Case 3 M S ♀ aged [illegible] years *O D* V A = 0 5 Incipient cataract Disc and field normal Tension 3[illegible]–34 mm Hg – *O S* V A = P/L Dense cataract Disc never seen State of field difficult to evaluate due to cataract Tension 30–25 mm Hg – Tension in O S in repeated measurements constantly lower than in O D

Comment Cataract more pronounced in the eye with the constantly lower tension

The five cases reported under paragraphs *3* and *4* above should hardly have influenced the results in either direction

Discussion

According to *Becker* and *Shaffer* (1965) the diagnosis primary open angle glaucoma cannot be established unless both eyes are affected All patients with unilateral open angle glaucoma should be suspected of having secondary

was questionable in the case of 13 patients since they had a pronounced visual loss due to other causes than cataract In two of these cases a bilateral visual loss was deemed to be explained by macular degeneration Ten patients had a visual loss in the glaucoma eye chiefly attributable to the glaucoma One patient had a visual loss in the reference eye due to macular changes after thrombosis Two of these 13 patients were judged to have a higher degree of cataract in the glaucoma eye and one to have a higher degree of cataract in the reference eye Since the visibility of the eye fundus through the undilated pupil seemed to have been about equally good bilaterally in these three cases, two of them were listed as "plus?" and one as "minus?" In the case of the remaining 10 "questionable" patients insignificant opacities had been observed in both eyes and the visibility of the eye fundus through the undilated pupil seemed to have been good bilaterally these patients were thus listed as "nought" Five of them could later be re examined and were then found still to have very insignificant bilateral cataracts to about the same extent in both eyes A fairly good evaluation could thus be made also of those retrospective cases in which the cataractous process could not be related to the decrease in visual acuity

In connection with Tables III and IV also the following comments should be made

1 In the examined group the type of cataract characterized by anterior subcapsular vacuoles and observed after treatment with strong cholinesterase inhibitors (cf *Axelsson* 1968 a) was found in only one case This patient had glaucoma of the type 2–0 and unilateral cataract In all other cases the cataracts found in the glaucoma eyes were of common senile types as a rule cuniform or nuclear or combinations of both All cases of bilateral cataracts exhibited the same type of opacity in both eyes There were thus no distinctive features differentiating the cataract in the glaucoma eye from that in the reference eye For the retrospective group a similar evaluation could not be made since in many cases the type of cataract present had not been specified in the records

2 In the examined group pseudo exfoliation of the lens capsule was always looked for Out of the 47 patients 8 had bilateral pseudo exfoliation whereas 14 showed no signs of pseudo exfoliation in either eye The remaining 25 patients (53 %) had pseudo exfoliation in the glaucoma eye but not in the reference eye An analysis of these 25 patients gave the following results in the reference eyes glaucoma of stage 0 was present in no less than 21 cases glaucoma of stage 1 in 2 cases and of stage 2 in 2 cases In the glaucoma eyes the distribution of the stages 2 to 5 was comparatively even Of these 25 patients with unilateral pseudo exfoliation 13 had clear lenses bilaterally 11 had bilateral cataract in 10 cases in the same degree in both eyes and in one case (listed as plus?) a slightly more pronounced cataract in the glaucoma

eye One patient had unilateral cataract in the glaucoma eye The investigation has thus not provided any convincing evidence in support of the concept that glaucoma when associated with pseudo exfoliation should predispose to cataract formation

3 As mentioned above two patients were excluded due to incomplete data on the state of the lenses One of them had asymmetrical glaucoma of the type 5–3 and one of the type 5–0 Since however the visibility of the eye fundus through the undilated pupil was good in both cases the state of the lenses was not likely to have been very different in the two eyes in any of these cases

4 As also mentioned above a classification of the glaucoma according to Table I could not be made in the case of three patients due to pronounced lens opacification in one eye These cases will be presented in detail below

Case 1 H H ♂ aged 8 years *O D* V A = c f 1–2 m Almost dense cataract Disc never seen State of field difficult to evaluate due to cataract Tension never exceeding ? mm Hg – *O S* V A = 0 9 Cataract Disc glaucomatous Field on routine examination normal Tension ?6–32 mm Hg Only O S treated

Comment Cataract more pronounced in the eye in which the presence of glaucoma could not be ascertained

Case 2 L E ♂ aged 73 years *O D* V A = 1 0 Incipient cataract Disc and field normal Tension ?0–?3 mm Hg – *O S* V A = c f 0.5 m Almost dense cataract Pseudo exfoliation Disc never seen Uncharacteristic field defect Tension ?5–3? mm Hg

Comment Cataract more pronounced in the eye with ocular hypertension

Case 3 M S ♀ aged ?1 years *O D* V A = 0 5 Incipient cataract Disc and field normal Tension 3?–34 mm Hg – *O S* V A = P/L Dense cataract Disc never seen State of field difficult to evaluate due to cataract Tension 30–25 mm Hg – Tension in O S in repeated measurements constantly lower than in O D

Comment Cataract more pronounced in the eye with the constantly lower tension

The five cases reported under paragraphs 3 and 4 above should hardly have influenced the results in either direction

Discussion

According to *Becker* and *Shaffer* (1965) the diagnosis primary open angle glaucoma cannot be established unless both eyes are affected All patients with unilateral open angle glaucoma should be suspected of having secondary

glaucoma Also *d Ombrain* (1949) is of the opinion that unilateral chronic simple glaucoma does not exist and that such glaucoma cases when observed are of traumatic origin In their studies of a large glaucoma population *Rohrschneider* and *Bauermann* (1957) on the other hand, did not find any evidence supporting d Ombrain s concept but drew the *conclusion that true unilateral* chronic simple glaucoma may occur although only in exceptional cases

As far as the present material is concerned no signs whatever of an abnormal intraocular pressure were found in the reference eye in no less than 63 % of the patients at the time of the initial diagnosis Some of these patients have later developed ocular hypertension also in the reference eye but a fairly large number of them have normal tension values even after a follow up period extending over some years One might thus be tempted to draw the conclusion that all the patients under study might in fact not have suffered from chronic simple glaucoma

There are however some arguments which may offer evidence that the patient population under study had chronic simple glaucoma This disease is characterized as a condition in which – in the absence of other antecedent or present eye disease – the optic nerve is slowly being damaged by an elevated intraocular pressure caused by an increase in the resistance of the outflow system and finally leading to total loss of function The material presented in this study did not include any eyes with signs of previous surgery trauma or inflammatory disease of the inner eye and all eyes had open chamber angles *All eyes that have been classified as glaucoma eyes* displayed an abnormal intraocular pressure by the criteria generally accepted for this condition The majority of the eyes (76 %) also displayed signs of optic nerve damage in many cases advanced with gross field loss Hence they meet the criteria established for eyes with chronic simple glaucoma, and since *it is* known that years may elapse between the first signs of glaucoma in one eye and the appearance of the disease in the contralateral eye it should be reasonable to presume that the patients under study did in fact represent cases of chronic simple glaucoma

All patients under study had asymmetrical glaucoma by the criteria established for this condition in many cases with a high degree of asymmetry, *and none* of them had been treated for glaucoma prior to the examination on which the evaluation of the lenses was based When comparing the eyes termed "the glaucoma eyes with those termed the reference eyes *vi* the eyes with less advanced glaucoma or no signs of the disease no appreciable difference was *found between the two groups with respect to the presence* of cataract or the degree and extent of cataract present The results were essentially the same both in the examined and the retrospective groups of patients It should be stressed however that the examination of the lenses had of course not been made with the same meticulous care in *the retrospective*

group as in the examined group and minor differences between the two eyes may have been overlooked It is also obvious that an evaluation of cataractous processes as made in a retrospective study cannot be regarded as fully reliable In those retrospective cases in which the reduction in visual acuity was exclusively due to the cataract and in which the acuity could thus be taken as a measure of the cataractous process present there was no essential difference in visual loss between the group of reference eyes on the one hand and the group of glaucoma eyes on the other hand In similar cases in the examined group there was as a rule good correspondence between the degree and extent of the cataract and the decrease in visual acuity Those retrospective cases in which the cataractous process could not be related to the reduction in visual acuity have been reported in detail (cf *Results*) and also in these cases no essential differences in the cataractous process in the two eyes were observed It should thus be justifiable to attach some weight of evidence also to the findings relating to the retrospective group Also from another point of view this group is of interest since these patients were examined at a time when the possible relationship between chronic simple glaucoma and cataract was not yet a subject of inquiry the examiners had no preconceived opinion and were thus not biased in their evaluations in either direction

In cases of chronic simple glaucoma years may elapse – according to *Goldmann* (1959) more than a decade – from the onset of ocular hypertension to the development of field defects It is reasonable to assume that this period is longer the more advanced the optic nerve damage We should thus be entitled to conclude that the material under study should include many patients who had had an abnormal intraocular pressure in one eye for many years If it should hold true that a longstanding ocular hypertension should gradually damage the lens then we ought to have noticed some signs of an increased cataract formation in the glaucoma eyes above all in those subgroups in which the asymmetry of the glaucoma was most pronounced i.e. the cases rated as 5–0 5–1 and 4–0 But this was not the case With one exception the cataracts observed in the thoroughly studied glaucoma eyes were of the common senile types and even in cases with gross field loss they did not differ from those found in the reference eyes Nor was there any conclusive evidence indicating that unilateral pseudo exfoliation when associated with glaucoma should cause an increased susceptibility to cataract formation Hence the present investigation as well as also the review of the literature presented above do not lend any support to the view that chronic simple glaucoma should predispose to or precipitate cataract formation.

As shown in previous papers (*Axelsson* and *Holmberg* 1966 *Axelsson* 1968 a b) eyes with chronic simple glaucoma being treated with potent cholinesterase inhibitors frequently develop a type of cataract characterized by anterior subcapsular vacuoles (ASCV) It has also been shown (*Axelsson*

1968 c) that this type of cataract may often lead to a distinct visual loss which may set in early sometimes even during the first year of treatment The present investigation has not furnished any evidence that such a frequent occurrence and such a rapid progression of cataract should be attributable to the glaucoma on the contrary it lends further support to the concept that this cataract is the result of a toxic action on the lens caused by the miotics used

Summary

The present investigation was undertaken to study the relationship between chronic simple glaucoma and cataract formation

Section I presents a review of the literature from which it appears

1) that cataract as a result of glaucoma often occurs in the degenerative stage of absolute glaucoma the so called cataracta glaucomatosa and may sometimes occur after acute glaucomatous attacks the so called cataracta disseminata subepithelialis glaucomatosa acuta

2) that cataract is a common consequence of glaucoma surgery but that there seems to be no evidence indicating that the glaucoma disease as such should favour the development of postoperative cataract

3) that no reliable statistical investigation clearly demonstrating that chronic simple glaucoma should predispose to cataract formation seems to have been published

Section II reports a study of 194 previously untreated patients with unilateral or "asymmetrical chronic simple glaucoma and the following conclusions are drawn *viz*

1) that the findings do not support the concept that chronic simple glaucoma should predispose to or precipitate cataract formation

2) that the cataract found in eyes with chronic simple glaucoma seems to be of common senile types

3) that the findings do not support the concept that pseudo exfoliation of the lens capsule should increase the susceptibility to cataract formation in eyes with chronic simple glaucoma and

4) that the frequent development and rapid progression of cataract *in eyes with*

chronic simple glaucoma observed in patients being treated with potent cholin esterase inhibitors can hardly have been caused by the glaucoma

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Method

The laser gas tube was constructed from commercial waterjacketed Cenco (West improved with T S joints) male female condenser colums 65 cm in length with a clear bore of 1 cm diameter (1) An aluminum center electrode was inserted in the middle of the gas tube The ends constructed of aluminum formed com bination electrodes and Brewster angle window holders for sodium chloride windows A gold coated mirror was used as the reflecting mirror a sodium chloride flat as the output Irtran lenses and reflecting optics were used for focusing Power measurements were made with a thermal equilibrium monitor (Fig 1)

Both eyes of 10 dutch rabbits were exposed to the beam of a CO laser beam. The exposure data were

No of Rabbit eyes	Power Density Watts cm²	Beam diameter *on cornea* mm	Exposure *time* sec
4	9	5	1
6	12	4	4
6	12 – 15	4	1
4	15 – 0	4	1

All but two animals were sacrificed within 6 to 8 days after exposure The enucleated eyes were studied by histological and histochemical techniques Two lenses of each *group were stained with Hematoxylin – Eosin (H & E)* and PAS (Periodic Acid Shiff reaction) Two corneae of each group were sectioned in the cryostat and examined for DPN diaphorase activity using the technique described in a previous article (2) Several sections were counterstained with H & E to allow for differentiation of enzyme activity of keratocytes from that of invading cells of hematogenous origin The *remaining* eyes were sectioned and stained with H & E PAS Masson trichrome and Alcian blue for acid mucopolysaccharides Two animals were observed clinically and one of these 12 W cm² 4sec was sacrificed after six months for histological examination One animal (1 15 W cm²-1 sec was still alive at the time of this report (J months post irradiation) being followed periodically by biomicroscopic examination

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OCULAR INJURY FROM CO LASER IRRADIATION

BY

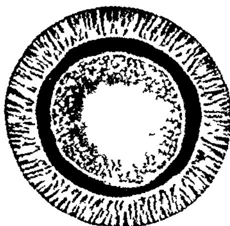
WALTER J GEERAETS M D BEN S FINE M D
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Generation of coherent electromagnetic radiation by stimulated emission utilizing solid state lasers liquid lasers and gaseous lasers extends spectrally from the ultraviolet to the far infrared The power range of such devices is from milliwatts to gigawatts They may be operated as pulsed lasers ranging from fractions of a nanosecond to several milliseconds or they may produce continuous radiation (CW) Their unique properties lie in their directionality monochromaticity and coherency

At the CO_2 laser wavelength (10 6 μ) biological structures transparent for the visible spectral range (400–750 nm) become opaque About 67 % of the incident energy of the CO laser energy is absorbed in the first 10 μ of tissue with which it interacts whereas atmospheric attenuation is relatively low in comparison with that at wavelengths of the visible spectral region These characteristics of CO_2 laser radiation may result in severe ocular injury primarily involving the cornea and possibly deeper within the anterior segment of the eye depending upon the energy and power densities and distribution on the cornea

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the center of the cornea remaining 9 months after exposure and only slight corneal thickening The lenses of both eyes appeared clear by gross examination at that time but there was a small central indentation of the anterior surface of both lenses still present though it was less marked than in the early post irradiation period By retroillumination from the fundus a ringlike density was visible measuring about 2 3 of the lens diameter Just inside this ring was a corona of fine dot like opacities (Fig 2) Under oblique illumination it appeared like a sharply demarcated zone within the anterior and posterior cortex which completely enveloped the central portion of the lens (Fig 3) and with the fine dust like opacities situated within and close to this demarcation zone The lenses were otherwise clear and the ocular fundus could be examined easily by ophthalmoscopy Subsequent histopathologica examination of serial sections of the entire corneae showed that no corneal perforation had existed thus ruling out lens injury due to corneal perforation



Fig

Draw ng [illegible] len as appearing with retroillum nati n The circle within the lens cortex represent the p r [illegible] h l utl ne of a hazy demarcation z ne extending through an erior and po te r [illegible] rtex mpletely envel ping the central lens portion Fine dust like pa t es ar [illegible] ible just inside this demarcation zone

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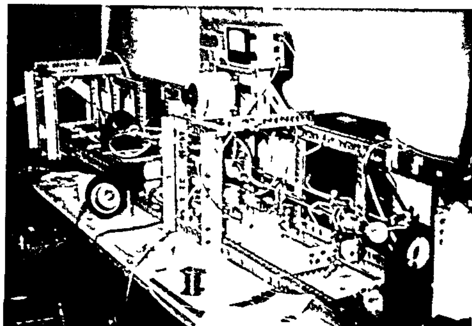


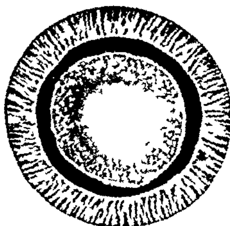
Fig. 1

Twenty watt CO_2 laser. Specifications as follows: active cavity length variable from two to four meters, 0.9 cm bore diameter, Brewster angle NaCl windows, mirror configuration variable – plane parallel and hemispherical, external beam coupling with uncoated NaCl reflector, 60 cycle excitation and overall efficiency P_{out}/P_{line} 6%.

Results

In vivo observations. All corneae showed grayish white opacities and several corneae of each group had deep central defects and or evidence of perforations. In all instances the exposed corneal area surrounding the central ulcerations was markedly thickened to about twice the normal thickness. An anterior chamber was present in all but two animals (12 W/cm – 4 sec). No cataracts had formed within the first week post exposure. In eyes where biomicroscopic examination of the lens was possible in spite of the corneal opacities the anterior lens surface appeared to be indended in its central portion, an observation reported by Fine et al. (5). The one rabbit still alive at the time of this report (12–15 Watts/cm – 1 sec) showed severe white opacities and thickening of both corneae, generalized cellular infiltration and conjunctival reaction one week post exposure. The lenses though difficult to examine appeared to be clear but featured the above mentioned indentation of the anterior lens surface. Over the next several months both corneae cleared gradually with only a small superficial haziness approximately 3 mm in diameter below

the center of the cornea remaining 9 months after exposure and only slight corneal thickening The lenses of both eyes appeared clear by gross examination at that time but there was a small central indentation of the anterior surface of both lenses still present though it was less marked than in the early post irradiation period By retroillumination from the fundus a ringlike density was visible measuring about 2 3 of the lens diameter Just inside this ring was a corona of fine dot like opacities (Fig 2) Under oblique illumination it appeared like a sharply demarcated zone within the anterior and posterior cortex which completely enveloped the central portion of the lens (Fig 3) and with the fine dust like opacities situated within and close to this demarcation zone The lenses were otherwise clear and the ocular fundus could be examined easily by ophthalmoscopy Subsequent histopathological examination of serial sections of the entire corneae showed that no corneal perforation had existed thus ruling out lens injury due to corneal perforation



Fig

Drawing of lens as appearing with retroillumination The circle within the lens cortex represents the peripheral outline of a hazy demarcation zone extending through anterior and posterior cortex completely enveloping the central lens portion Fine dust like opacities are visible just inside this demarcation zone



Fig 3

Slitlamp photography of the same lens as shown in Fig 1 Note the rather sharp demarcation line within anterior and posterior cortex and the granulation effect within the cortex of the lens close to the demarcation zone as seen with oblique slit illumination

Histopathology

One week post irradiation The histopathology for all eyes examined can be described jointly since there was no significant difference in tissue reaction for the different power densities (watts/cm) and exposure times (1 sec and 4 sec) except for some minor degrees in severity of the lesion The corneae of all eyes enucleated early after exposure were very thin in the central portion down to Descemet s membrane and in a number of eyes a central perforation existed In these the perforation was plugged by iris and a fibrinous exudate in the anterior chamber The corneae showed marked cellular infiltration and early vascularization Thick organized fibrinous deposits were attached to the inner surface of the cornea The region between the deep ulceration and the periphery showed marked thickening (Fig 4 a) This area of corneal thickening showed loss of staining affinity to alcian blue for demonstration of acid mucopolysaccharides though there were still islands of the stroma in this region which stained Descemet s membrane which had been interrupted

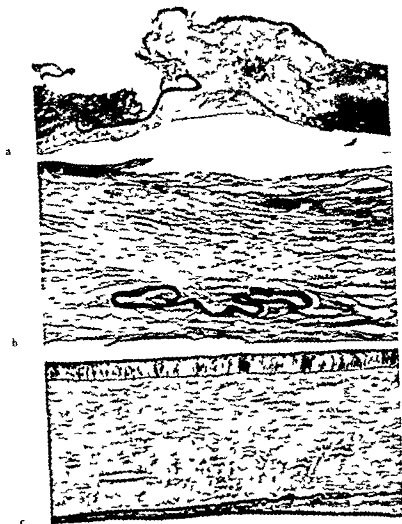


Fig 4 (a b & c)

(a) Thickening of the cornea adjacent to central ulceration and or perforation PAS × 35
(b) Remnants of descemet's membrane imbedded within the corneal stroma (*6 months* post irradiation) PAS × 100
(c) Doubling of *Descemet's membrane* (6 months post irradiation) PAS × 100

in the central perforation was found curled up along the edges and was imbedded in the retrocorneal fibrous membrane Small pieces of Descemet's membrane were observed imbedded in the corneal stroma even six months post irradiation (Fig 4 b) and duplication or splitting of Descemet's membrane was clearly visible (Fig 4 c)



Fig 3
Slitlamp photography of the same lens as shown in Fig 1 Note the rather sharp demarcation line within anterior and posterior cortex and the granulation effect within the cortex of the lens close to the demarcation zone as seen with oblique slit illumination

Histopathology

One week post irradiation The histopathology for all eyes examined can be described jointly since there was no significant difference in tissue reaction for the different power densities (watts/cm) and exposure times (1 sec and 4 sec) except for some minor degrees in severity of the lesion The corneae of all eyes enucleated early after exposure were very thin in the central portion down to Descemet s membrane and in a number of eyes a central perforation existed In these the perforation was plugged by iris and a fibrinous exudate in the anterior chamber The corneae showed marked cellular infiltration and early vascularization Thick organized fibrinous deposits were attached to the inner surface of the cornea The region between the deep ulceration and the periphery showed marked thickening (Fig 4 a) This area of corneal thickening showed loss of staining affinity to alcian blue for demonstration of acid mucopolysaccharides though there were still islands of the stroma in this region which stained Descemet s membrane which had been interrupted

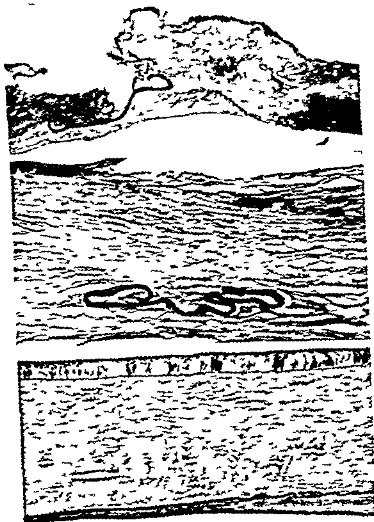


Fig 4 (a b & c)

a Thickening of the cornea adjacent to central ulceration and or perforation. PAS × 35

b Remnants of descemet's membrane imbedded within the corneal stroma (6 months post irradiation) PAS × 120

(c) Doubling of Descemet's membrane (6 months post irradiation) PAS × 120

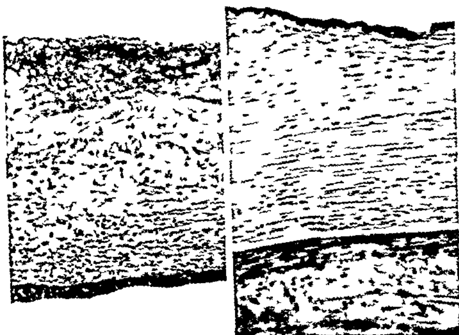
in the central perforation was found curled up along the edges and was imbedded in the retrocorneal fibrous membrane Small pieces of Descemet's membrane were observed imbedded in the corneal stroma even six months post irradiation (Fig 4 b) and duplication or splitting of Descemet's membrane was clearly visible (Fig 4 c)



Fig 3
Slitlamp photography of the same lens as shown in Fig 1 Note the rather sharp demarcation line within anterior and posterior cortex and the granulation effect within the cortex of the lens close to the demarcation zone as seen with oblique slit illumination

Histopathology

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b

Fig 6 (a & b)

Cornea adjacent to section shown in Fig 5 In Fig 6 a the stroma is irregular and stromal lamellae cannot be clearly made out In Fig 6 b the stroma can be made ut and approaches more the organization of normal corneal architecture and the stromal lamellae appear more thickened and glued together (Masson trichrome X 13o)

post exposure The irides showed little involvement except for a mild hyperemia and some exudate where corneal perforation had taken place Retinal damage was not observed in these eyes

Sections stained for DPN – diaphorase activity of eyes enucleated one week after exposure revealed the typical increase in enzyme activity as had been described by Kaufman et al (4) in their work on enzyme activity in corneal repair after cellular destruction by freezing The increase of enzyme activity in the more superficial layers of the corneal stroma as seen in normal non irradiated corneae was enhanced in areas of laser irradiated stroma (Fig 7 a) This increase of greater concentration of oxidative enzymes as evidenced by greater affinity to the nitroblue tetrazolium stain is accepted as a sign of the healing process A very strong increase in enzyme activity was located within

In the thickened area immediately adjacent to the central ulceration there were areas of structureless, homogenous material surrounded by small vacuoles and regenerating vascularized tissue (Fig 5) More peripherally but still within the area of the thickened cornea the stromal lamellae seemed to be *glued together as evidenced by the lack of artifactual separation and cleft* formation usually seen after corneal tissue processing (Fig 6 a & b)

Though the original repair of the corneal defect seemed primarily achieved by fibrous ingrowth the sections obtained from eyes enucleated 6 months after irradiation indicated that stromal proliferation had taken place This was apparent from the morphological structure and the similar staining characteristics with the various stains used in this study It also was supported by the clinical observation of gradual clearing of the cornea over several months

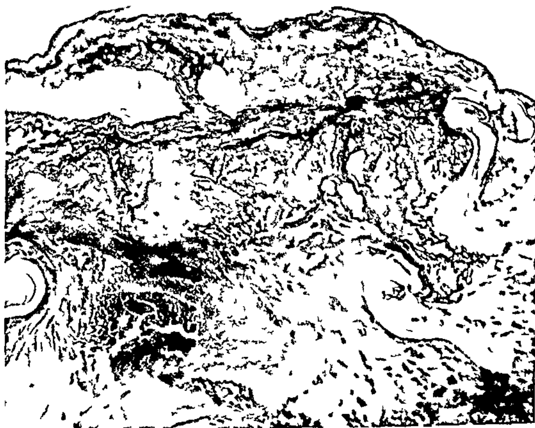
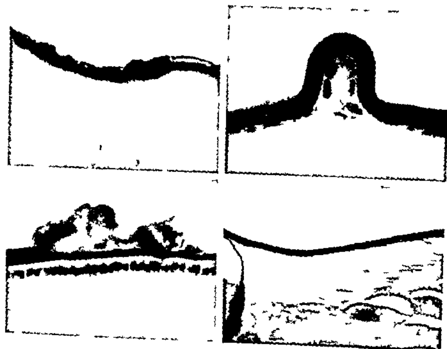


Fig 5

Thickened area of the cornea immediately adjacent to central ulceration (Masson trichrome × 135) Note curled edge of Descemet s membrane Homogenous material surrounded by reticulated and vacuolated structures



b

d

Fig 8 (a b c & d)

(a) Iris pigment deposit on lens capsule (PAS × 220)

(b) Fold in anterior lens capsule (Masson trichrome × 550)

(c) Thickening of anterior lens capsule with fibrinous deposits and iris pigment granules (PAS × 220)

(d) Absence of staining with PAS in anterior lens cortex in area underneath iris pigment deposits (not visible in this photomicrograph) PAS × 140

Discussion

The absorption coefficient is high at the CO wavelength (10 6 μ) both for tissues essentially opaque at visible wavelengths and for those such as the cornea transparent at visible wavelengths Consequently the ocular effects produced by CO laser irradiation differ from those observed after irradiation at visible wavelengths where the primary target site is the retina Many of the features observed can be explained on a thermal basis predicated on the high absorption coefficient of the cornea for the CO laser wavelength since about 67 % of the energy incident on the cornea is absorbed within the first 10 μ of tissue The absence of corneal staining with alcian blue for acid mucopolysaccharide one week after injurious exposure may be explained by heat denatura

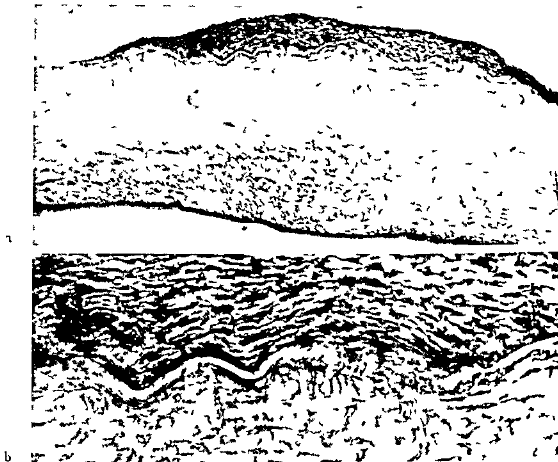


Fig 7 (a & b)

(a) DPN diaphorase activity of the exposed rabbit cornea one week after CO laser irradiation (× 35) Note the increase of enzyme activity in the superficial stromal layers and within the organized fibrous tissue underneath Descemet's membrane
(b) higher magnification of Fig 7 a

the fibrous tissue attached to the deep surface of the irradiated portion of the cornea (Fig 7 b) This should be expected because of the numerous hematogenous cellular elements present in this zone of tissue repair

All lenses had pigment granules from the iris adherent to the lens capsule (Fig 8 a) There were areas of fibrous adhesions and folds in the lens capsule (Fig 8 b) Indentation of the anterior lens surface was seen and the lens capsule seemed to be thickened in some sections (Fig 8 c) There was also some loss of affinity to the PAS stain in the cortical region immediately underneath the capsule where the iris pigment had been glued to the capsule (Fig 8 d) However within the limitations of the applied examination techniques the lens epithelial cells appeared to have remained unchanged

of these lesions it may be assumed that these opacities represent the expression of minimal unspecific non progressive lenticular injury This assumption is speculative and will need clarification by more refined basic experimental techniques and considerably greater numbers of observations After studying the more severe pathological changes as described in this report more subtle changes of threshold and near threshold injury are under investigation More recent data by Fine and co workers (7) have shown that irradiation of the rabbit cornea for 30 min at a power density of 0 1 W/cm did not result in any demonstrable injury while at 0 15 W/cm² anterior corneal changes could be detected

Summary

Ocular effects of CO laser irradition (10 6 μ) have been investigated by biomicroscopic follow up and by histochemical and histological techniques Power densities incident on the cornea ranged from 9 to 20 watts/cm Most severe damage occurred within the exposed corneae with central ulcerations and perforations and with extensive thickening of the cornea in regions adjacent to the central defects Iris changes were mild The lenses of the exposed eyes showed a number of peculiar changes which in the early stages post irradiation seemed to be restricted to the anterior lens capsule and cortex However later biomicroscopic observations (9 months post irradiation) revealed lens changes involving the posterior cortex as well without having resulted in marked cataractous changes

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tion and can be compared with similar findings after retinal thermal injury (5) caused by retinal exposures to radiation within the visible spectrum Thermal damage to deeper structures of the anterior segment of the globe caused by the CO_2 laser irradiation are due presumably to heat conduction from the site of major absorption in the cornea rather than by heat generation within these structures themselves by conversion of the radiating energy into thermal energy This also explains the minimal morphological changes in the well vascularized iris for blood at these relative long exposure times dissipates most of the heat conducted to the iris from the cornea Absorption within the iris pigment cells does not play the role it does in thermal injury caused by visible light where the iris pigment is a primary site of light absorption and resulting heat generation by light transmitted through the cornea and aqueous humour

The effects observed on the anterior lens surface and within the anterior cortex of the lens are more difficult to explain Damage by heat conduction from the cornea and through the anterior chamber may be accepted as the cause for some of the early changes since the lens does not possess the cooling system of blood flow as does the iris The lack of cataractous changes is surprising particularly since iris exposure to intense visible light causing iris coagulation results in localized lens opacities which usually remain stationary

The indentation of the anterior lens surface might best be explained on a mechanical basis if very short exposure flashes of high power densities had been used However with the relative long exposure times as used in this experiment this mechanism becomes unlikely Further investigation possibly using high speed kinematography may shed some light on this questionable mechanical factor of lens injury Another explanation is more likely namely that of "shrinkage of denaturated protein structures of the anterior cortex of the lens similar to that seen in the retinal receptor cell layer after retinal thermal injury (2) This then could be the reason for the folds in the lens capsule too The lack of permanent lens opacities however leaves this assumption open to question In cases where corneal perforation occurs during exposure and hence loss of the anterior chamber suddenly arrises direct irradiation of *the anteriorly displaced lens takes place plus the effect of heat conduction* from the exposed cornea These two factors could in this instance cause the lens injury though only submitted as a theory at this place

The late clinical finding of a corona of fine dust like opacities within an optically hazy demarcation zone within the anterior peripheral and posterior cortex itself is of interest since in these eyes positively no corneal perforation took place during or following exposure Similar fine opacities have been observed in the rabbit lens after low dose x ray irradiation (6) although in those eyes the lenticular changes were restricted to the posterior cortex of the lens in close proximity to the posterior suture line Though it is not intended to indicate here that there may be an etiological connection in the production

The Eye Hospital and The Department of Serology and Bacteriology University of Helsinki

THE EFFECT OF HOMOLOGOUS ANTILYMPHOCYTIC SERUM ON RABBIT CORNEAL HETEROGRAFTS

BY

S VANNAS L MERENMIES A TIILIKAINEN and M VANNAS

Antilymphocyte and thymocyte antibodies can produce lymphopenia and also suppress delayed hypersensitivity reaction (*Waksman* et al 1961 *Russe* and *Crowle* 1965) Antilymphocytic serum[1]) has markedly prolonged the survival of skin homografts in experimental animals and renal homografts in man (for references see e g *Starzl* et al 1967 *Monaco* et al 1966) observed a prolonged survival time of heterografts also Antithymocyte serum was stated to produce more persistent lymphopenia than antilymphocyte serum (*Nagaya* and *Sieker* 1965)

In the rabbit a homograft reaction seldom occurs after corneal homotransplantation, although it can be provoked for instance by a skin transplant from the same donor (*Maumenee* 1955) On the other hand heterografts always cause a pronounced corneal reaction in the rabbit (e g *Vannas et al* 1969)

The present experiments were designed to study the effect of homologous anti lymph node or anti thymus serum on the heterograft reaction to rabbit cornea

Material and Methods

General plan of the experiment

Interlamellar corneal grafts were transplanted from calves to 41 albino rabbits of both sexes weighing 2.1 ± 0.2 kg at the beginning of the experiment

This work has been aided by grants from The Sigrid Juselius Foundation, Helsinki

[1]) The term antilymphocytic serum will be used to connote the heterogeneous group of antisera reacting with the nucleated *cells of* an individual regardless of the kind of cells used as immunogen

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R e ve l J ne 1st 1968

Four rabbits were excluded because of infection in the first few days after the operation

From the day of operation ten rabbits were given a daily intravenous injection of homologous anti-lymph node serum (ALS) ten were given anti thymus serum (ATS) nine were given normal rabbit serum (NRS) In all cases the dose was 1 5 ml/kg Eight rabbits were not given serum The treatment lasted 4–6 weeks For practical reasons the experiments were divided into three successive series

Peripheral blood samples were taken from the recipients prior to grafting twice on the day of transplantation and then twice weekly for total and differential leucocyte counts and haematocrit determinations

The condition of the eyes was followed under the biomicroscope (Haag Streit) Most of the rabbits were killed after 4–6 weeks and their eyes were enucleated for histologic study The animals were autopsied The thymus and mesenteric lymph nodes were examined macroscopically and microscopically Samples for histology were fixed in formalin Paraffin sections were stained with haematoxylin eosin

Technique of transplantation

The grafts were taken from fresh calf eyes enucleated not more than four hours earlier and stored at + 4° C The eyes were kept in penicillin 20 000 IU/ml of saline for 20–30 min before grafting The operations were made under nembutal anaesthesia A limbal incision was made from 10–2 o clock just below the upper vessel plexus and an interlamellar pocket was prepared with a spatula in the upper cornea A whole thickness graft of 4 mm was then placed in this pocket The wound was sutured with two or three appositional stitches

Preparation and assay of ALS and ATS

Five albino rabbits weighing about 3 kg were used They received weekly intramuscular and subcutaneous injections in the lower back of pooled rabbit tissue homogenate containing equal volumes of a 20 per cent saline suspension of homogenized rabbit thymus or mesenteric lymph nodes and Freund s incom plete adjuvant Initially two of the rabbits were immunized without adjuvant (without success) The details of the immunization are shown in Table I

The animals were first bled after eight weeks immunization and bleeding lasted for 16 months in all Usually (Table II) one day before the antigen injection 50 ml of blood were taken from the central ear artery using sterile techniques The serum was separated aseptically and stored at − 20° C until used

Table I

The details in the immunization schedule

Number of rabbits	Immunizing mixture used 0–4 mo	Amount ml	Immunizing mixture used 4–8 mo	Amount ml	Immunizing mixture used 8–16 mo	Amount ml
R 1111	lymph node h + adjuvant	3+3	lymph node h + adjuvant	3+3	lymph node h + adjuvant	1+1
R 1112	lymph node h	3	lymph node h + adjuvant	3+3	lymph node h + adjuvant	1+1
R 1113	thymus h	3	thymus h + adjuvant	3+3	thymus h + adjuvant	1+1
R 1114	thymus h + adjuvant	3+3	thymus h + adjuvant	3+3	thymus h + adjuvant	1+1
R 1115	thymus h + adjuvant	3+3	thymus h + adjuvant	3+3	thymus h + adjuvant	1+1)

) Exsanguination after 10 months

Consecutive bleedings from the immunized animals were tested for antibody using the lymphocytotoxicity test After the appearance of lymphocytotoxic antibodies the rabbits were bled at one to four week intervals to collect serum for clinical experiments and the serum samples were checked for antibody production Because pooled serum was administered to the transplanted animals pooled samples were sometimes tested serologically

The cytotoxic ty test was as described by *Amos* (*1966*) with slight modifications For each test rabbit lymphocytes were collected from 3–4 randomly selected normal animals The heparinized blood was mixed with Plasmagel (Roger Bellon Seine) in the ratio 10 3 One ml of high titred human anti A serum (heated for 30 min at 56) was added to each 10 ml of blood to accelerate erythrocyte sedimentation For the same purpose the mixture was allowed to settle in large glass tubes in which the blood column was only some 3 cm high (*Hulliger* and *Blazkovec 196*) The leucocyte rich supernatant plasma was treated according to the improved method of Amos (personal communication 19) which includes *red cell* haemolysis by NH_4Cl as suggested by *Boyle* (196) As complement we used normal rabbit serum and guinea pig serum the latter being absorbed with an equal volume of washed pooled rabbit red cells (incubation for 1 hr at 4 C) Rabbit complement produced weaker results in the cytotoxicity test than did guinea pig complement If the trypan blue exclusion test indicated *the death of less than* 20 per cent of the lymphocytes the test was considered negative

Table II
Lymphocytotoxicity of the Sera

Date of testing	bleeding	Bleeding No	Serological evidence of cytotoxic antibody in rabbit No				
			1111	1112	1113	1114	1115
Sept 28 66	Sept 22 66	I	-	-	-	-	-
Dec 2 66	Nov 30 66	II	-	-	-	+	(+)
	Feb 14-15 67	III	++	(+)	-	+	+
Mar 8 67	Feb 21-23 67	IV	++	-	-	+	+
Mar 17 67	Mar 1 67	V	+	+	-	+	-?
	Mar 7 67	VI	+	(+)	-	(+)	-
	Mar 31 67	VII	-	-	-	X	-?
Apr 26	Apr 8 67	VIII	-		X	X	X
Aug 7	Apr 15 67	IX	(+)		-	(±)	
	Apr 24 67	X	(+)	-	-	(+)	
	Jun 1	XI	-?	-	-	-	-
	Jun 12	XII	+		-		
Aug 21	Jun 22	XIII	X		X		
Aug 30	Jun 29	XIV	+		-		
	Jul 6	XV	++	+	-	-?	
	Jul 13	XVI	++	++	(+)	X	
	Jul 13	XVI	++	-	-	-	
	Sept 11	XVII	-	-	-	-	
Nov 10	Oct 10	XVIII	(+)	X	X	X	
	Oct 12	XIX	X	+	-	-	
	Oct 26	XX	+	-	-	-	
	Oct 26	XX	+	++	-	-	
	Nov 10	XXI	+	X	+	+	
Dec 28	Nov 22	XXII	+	+++	+	++	
	Nov 29	XXIII	-?	++	X	X	
	Dec 7	XXIV	(+)	++	-	++	

Results

In vitro characteristics of ALS and ATS

Table II presents a survey of the antibody titrations Evidently all the rabbits produced cytotoxic antibodies although these were not observed in some bleedings This may have been because the antibody was depleted by repeated bleeding (for instance see rabbit 1111 tests run on Nov 10 and Dec 28 rabbit

1119 tests on Dec 28) or because the specific antigen(s) were locking in the lymphocyte pool used in some tests

Individuals varied in their ability to produce antibody Rabbit 1113 appeared to be a fairly poor antibody producer rabbits 1111 and 1112 were reasonably stable antibody producers and 1114 was only slightly inferior to them

The consistency of antibody production was greatest in the animals that produced the highest titred antisera Maximum titre for anti lymph node sera 1111 and 1112 was 1 16 for anti thymus serum 1114 it was 1 8 and for anti thymus serum 1113 1 4

The first serological evidence of cytotoxic antibodies was seen after four months immunization with thymus homogenate Lymph node homogenate initially induced weaker antibodies but in the long run was at least as effective as the thymus material

Clinical behaviour of the corneal heterograft (Fig 1)

Controls The first symptoms of a heterograft reaction – incipient vascularization and sensitivity to light – appeared after 8–14 days (mean 12 days) in the untreated group and 7–16 days (mean 12 days) in the group given NRS New vessels grew in the superior part of the bulb across the limbus and the wound area and soon reached the margin of the transplant

After 14 days three quarters of the untreated animals displayed oedema in the vascular area in the upper part of the cornea and a gray sickle shaped region which bordered on the upper margin of the graft and soon surrounded the graft entirely

The reaction began and proceeded similarily in the NRS and untreated groups However its intensity was possibly somewhat weaker in the NRS treated group

Opacification of the heterograft (Fig 1) began after two weeks in five out of eight untreated rabbits and five out of nine rabbits given normal serum Opacification began in two further rabbits of each group after three weeks and in the remaining animals after four weeks Thus the NRS and untreated groups did not differ markedly in this respect

The inflammatory symptoms increased further and the transplants of the control groups were opaque after 3–6 weeks (Figs 2 and 3) and often invisible because of the profuse vascularization and opacification of the surrounding cornea

ILS and ITS treated groups – The first inflammatory symptoms in the rabbits receiving immune serum generally appeared in the third week If a heterograft reaction set in its intensity was weaker on the whole than in the controls The new vessels were delicate and fewer in number and corneal oedema was also milder Opacification of the transplant spread the top down

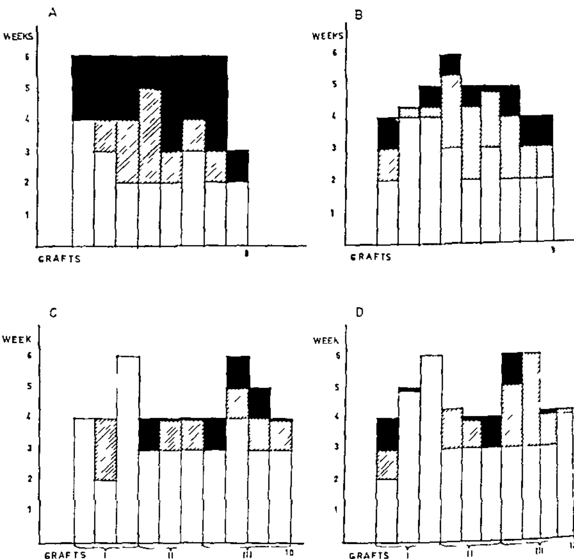


Fig. 1

Opacification of the interlamellar corneal heterografts from calves to rabbits. A Untreated group. B Group treated with normal rabbit serum. C Group treated with homologous anti thymus serum. D Group treated with homologous anti lymphnode serum. ▭ Slight opacification ■ Opaque

wards and the lower part of the graft was still frequently clear after 5–6 weeks although the upper part was covered by a superficial semitransparent fibro vascular membrane

The heterograft began to cloud after two weeks in one of the ten animals given ATS after three weeks in a further six animals and after four weeks in one case (Fig 1) No opacification was seen in two animals during the 4–6 weeks observation period (Fig 4)



Fig °
Totally opaque and heavily vascularised corneal heterograft of untreated rabbit after 6 weeks



Fig 3
I annusl ke vasculartsation and opacification of heterograft treated with normal serum for 6 weeks

Graft opacification was roughly similar in the rabbits given ALS Opacification was seen in one rabbit after two weeks seven after three weeks eight after four weeks and after five weeks nine out the ten animals had some opacification (Fig 5)

Opacification of the graft was thus delayed as compared with the control groups In both the ALS and ATS group two grafts were clear after four weeks and one graft after six weeks The transplant was completely clouded during the observation period in six (60 per cent) animals of the ATS group

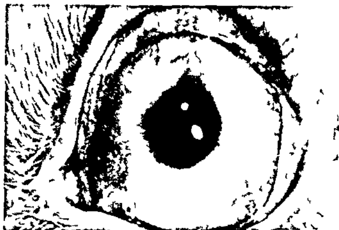


Fig 4
Clear corneal heterograft of rabbit treated daily with ATS for 6 weeks

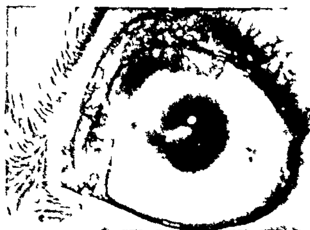


Fig 5
Almost clear at lower border clouded corneal heterograft Vascularisation in the upper part of the cornea Daily treatment with ALS for 6 weeks

and three (30 per cent) of the ALS group It was partly clouded in a further eight (two ATS six ALS) animals

Histologic appearance

The histologic preparations showed that the heterografts had remained in situ In three out of 37 cases an open communication led from the heterograft to the corneal surface always accompanied by marked inflammatory changes

The inflammatory changes were severe in the control series except in one animal treated with normal serum *Pronounced inflammatory cell infiltration* was established around the transplant (Figs 6 and 7) closest to the transplant were granulocytes (which always display eosinophilic granulation in the rabbit) with a dense zone of lymphocytes immediately beyond Vascularization was fairly heavy close to the margin of the transplant There was often necrosis macrophages and fibroblast proliferation at the margin The graft itself displayed granulocyte infiltration and oedema

The intensity of the graft reaction varied between individual animals especially in those treated with ALS or ATS In each group two animals showed minimal inflammation In these cases there was no oedema in the transplant *but a slight fibroblast proliferation at the margin* and a few lymphocytes in the surrounding cornea Granulocytes were almost completely absent (Fig 8)



Fig 6

Massive infiltration of polymorphonuclear and mononuclear inflammatory cells round the partly necrotic heterograft after 6 weeks No *treatment* The same cornea as in Fig [illegible] Magn × 80



Fig 7
Moderate inflammatory reaction with abundant vessels and mononuclear cells round the heterograft Daily treatment with normal serum for 6 weeks after operation The same cornea as in Fig 3 Magn × 80

In the other eight animals of the ATS group the reaction was strong In the ALS group five rabbits displayed a slight or moderate (Fig 9) and only three a strong reaction

The effect of ATS and ALS on the peripheral lymphocyte count and on the structure of the thymus and lymph nodes

Neither ALS nor ATS therapy had any detectable effect on the peripheral lymphocyte count either six hours after the first injection or later

Sixteen rabbits were autopsied The thymuses and lymph nodes of the anti body treated groups did not differ microscopically or macroscopically from those of the control groups



Fig 8
Heterograft practically without inflammatory reaction 6 weeks after operation Daily treatment with ATS The cornea is the same as in Fig 4 Magn × 80

Complications of serum therapy

One rabbit treated with ALS began to lose weight after four weeks and died in the fifth week At autopsy the cause of death could not be determined because of advanced autolysis but som findings suggest renal failure

No other complications were observed during the 4–6 weeks of serum therapy

Discussion

The beginning of the heterograft reaction in the rabbits treated with ALS and ATS was delayed as compared with the controls The transplants were opaque in all the controls after 3–6 weeks and histologically the inflammatory reaction

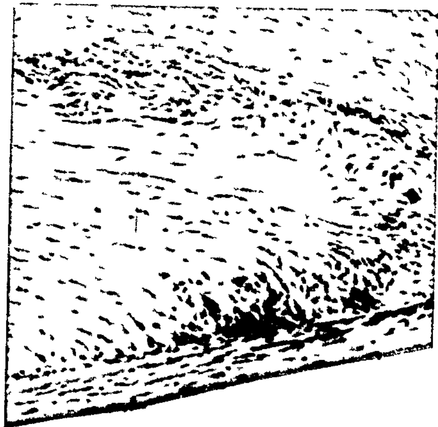


Fig 9
Mild inflammatory reaction at the border of the heterograft Daily treatment with ALS for 6 weeks after operation Same cornea as in Fig 5 Magn × 80

was pronounced The individual variation in the antibody treated groups was considerable The transplant was clear or slightly clouded in one third of the animals completely or partly clouded in the rest

There was less clouding of the heterograft in the ALS series than in the ATS series The results appeared to be correlated with the in vitro cytotoxic of the antisera The experiments were performed in three successive series

In the first and third series the ALS and ATS groups were roughly comparable however in the second series the animals in the ATS group gave poor results High titred antisera (from rabbits 1114 and 1115) were given to series I For practical reasons a serum pool with a lower antibody titre had to be given throughout the treatment of series II The treatment of series III was also begun with this low titred antiserum

Lymphopenia resulting from treatment with anti lymphocytic serum has been observed by several workers (*Waksman* et al 1961 *Russe* and *Crowle* 1965

Gray et al 1966 and many others) and stated insignificant by others (*Woodruff* and *Anderson* 1965 *Levey* and *Medawar* 1966) Considerable individual variation among the recipients has also been noted (*Iwasaki* et al 1966) At present the way in which antilymphocytic serum affects peripheral lymphocytes and the central reticuloendothelial tissue is not very clear Long term administration of antilymphocytic serum results in generalized lymphoid hyperplasia but the immunosuppression is not an enhancement phenomenon (*Levey* and *Medawar* 1966) *Abaza* et al (1966) have shown that depletion of peripheral lymphocytes cannot explain the immunosuppression

We observed neither lymphocytopenia nor histological changes in the mesenteric lymph nodes and thymus Our animals were probably not kept alive long enough for hyperplasia to occur although the use of homologous antiserum may partly explain the result Homologous serum will undoubtedly produce fewer side effects and be less immunogenic to the graft recipient than are the heterologous sera or serum fractions so far investigated

The in vivo effects of homologous antilymphocytic serum deserve further investigation *Parke* (1968) could not demonstrate a correlation between the in vivo effect and different in vitro tests of heterologous antilymphocytic serum in contrast to the observations of *Woodruff* et al (1967) Our results suggest that there is a correlation between the cytotoxicity test in vitro and the in vivo effect of homologous antiserum However comparisons are hampered by the weak cytotoxic effect in vitro which appears to be characteristic of isospecific antilymphocytic sera even after long periods of immunization A still closer correlation would be expected if homografts were protected with homologous antilymphocytic serum exhibiting appropriate isospecificity It remains to be seen whether this appropriate isospecificity has to be directed against the host s or the graft s genetic factors The prolongation of heterograft survival with homologous ALS in our series suggests that antibodies against the host s lymphocyte antigens are more important This is in agreement with the results of *Monaco* et al (1966) who prolonged heterograft survival with heterologous antilymphocytic serum

Summary

Calf cornea was transplanted interlamellarly to 3← albino rabbits Ten animals were given homologous anti lymph node serum (ALS) intramuscularly dose 1 5 ml kg day ten were given a corresponding dose of homologous anti thymus serum (ATS) nine were given normal rabbit serum and eight received no treatment

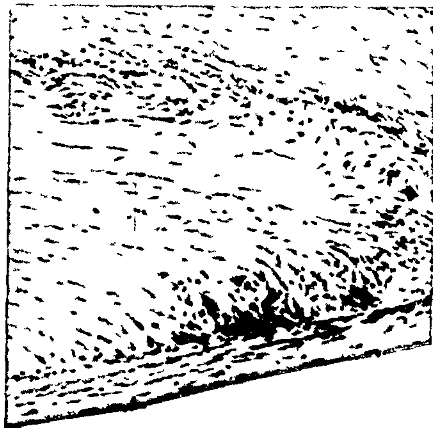


Fig 9
Mild inflammatory reaction at the border of the heterograft Daily treatment with ALS *for 6 weeks after operation Same cornea as in Fig 5 Magn* × 80

was pronounced The individual variation in the antibody treated groups was considerable The transplant was clear or slightly clouded in one third of the animals completely or partly clouded in the rest

There was less clouding of the heterograft in the ALS series than in the ATS series The results appeared to be correlated with the in vitro cytotoxic of the antisera The experiments were performed in three successive series

In the first and third series the ALS and ATS groups were roughly comparable however in the second series the animals in the ATS group gave poor results High titred antisera (from rabbits 1114 and 1115) were given to series I For practical reasons a serum pool with a lower antibody titre had to be given throughout the treatment of series II The treatment of series III was also begun with this low titred antiserum

Lymphopenia resulting from treatment with anti lymphocytic serum has been observed by several workers (*Waksman* et al 1961 *Russe* and *Crowle* 1965

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The heterograft reaction was delayed in the ALS and ATS groups compared with the controls but the suppression was usually not total

The antibody concentration of immune serum seemed to be positively correlated with its immunosuppressive effect

No lymphocytopenic effect was observed

These results and those published earlier concerning the significance of immune serum in immunosuppression indicate the necessity of further experimental work before clinical use

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In rare cases more than one retinal site is affected with normal intervening retinal tissue *Reese* (1956) *Maggi* (1963) *Paufique* (1964)

This relatively rare disorder is not accompanied by other occular abnormalities and it is not part of a generalized disease It is commonest among young men and is usually unilateral *but bilateral cases have been described* *Sugar* (1958) *Gronwall* (1961) *Woods* and *Duke* (1963) *Frenkel* and *Pusse* (1967) *In a study of 61 patients 39 men and 22 women* *Leber* (1916) found that the length of life in 80 % was less than 25 years

Reese (1956) considers the disorder to be essentially stationary with spontaneous vitreous hemorrhages without serious secondary changes while others consider it to be progressive e g *Leber* (1916) *Tour* (1957) *Sugar* (1958) *Maggi* (1963) and leading at times to retinal detachment cataract atrophy or glaucoma *Leber* (1916) *Reese* (1956) *Manshot* (1967)

The retinal disorder described by *Coats* in 1908 was separated by him into three groups Cases without gross vascular disease of the retinal vessels C...es with gross vascular disease and A very peculiar group which is characterized by the formation of large arteriovenous communications In 1912 he combined *the first two groups into one group and excluded the third* which today bears von Hippel s name

It is still discussed whether Leber s retinal degeneration with miliary aneurysms is a separate disorder or merely a preliminary stage or variant of Coats original second group a hypothesis suggested by Leber himself in 1912

Most investigators now agree with Leber *Junius* (1934) *Reese* (1956) *Tour* (1957) *Sugar* (1958) *Maggi* (1963) *Manshot* (1967) *Wise* (1957) Wise however later changed his view (*Wise* 1963) considering that Leber s disorder was a preliminary stage of Coats original third group *Paufique* (1964) believes that such a relation between Coats and Leber s disorder is questionable but states that the two disorders can possess certain similarities

Development *from* Leber s to Coats *disease has been described by Reese* (1956) who mentions two cases and by *Sugar* (1958) and *Gronwall* (1961) who each mentions one case

There is not complete agreement as regards etiology but most authors consider the vascular changes to be primary and the other ocular findings to be merely secondary manifestations *Leber* (1912) *Junius* (1934) *Reese* (1956) *Tour* (195) *Sugar* (1958) *Maggi* (1963) *Wise* (1963) *Paufique* (1964) *Henkind* and *Morgan* (1966) and *Manshot* (196)

Leber was not able to demonstrate a specific cause of the disorder but he believed that the primary vascular *changes were of* embolic origin perhaps the result of an endocarditis lenta (subacuta bacterial endocarditis)

Since then various investigators have tried to relate Leber s *disease to a* series of other conditions such as Osler s disease or hereditary hemorrhagic telangiectasia (*Junius* 1934) hypercholesterolemia (*Woods* and *Duke* 1963)

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LEBER S RETINAL DEGENERATION WITH MILIARY ANEURYSMS

BY

J K WEGENER

In 1912 Leber described a retinal disorder which he called retinal degeneration with multiple miliary aneurysms" Clinically Leber s disorder is characterized by being localized to a relatively circumscribed area usually in the periphery of the retina and by consisting of slightly elevated white intraretinal exudates over which one to several saccular and fusiform dilatations may be found terminally in the blood vessels which is itself often slightly dilated

These aneurysmal changes which vary in width from 2 to 4 times the size of the adjacent vessels are often grouped in small clusters lying superficially in the retina usually in the equator region or peripheral to it

There are in addition retinal hemorrhages vascular anastomoses neovascularization and sheathing of the vessels *Sugar* (1968) considered these changes characteristic even though they are not obligatory The retinal exudates which vary in colour from white to green are accompanied by tiny hard circumscribed exudates typically located in a circinate manner around the macula but may also be found at sites distant from the vascular changes

The character of these aneurysmal dilatations is still under discussion Some authors e g *Leber* (1912) *Tour* (1957) *Maggi* (1965) *Paufique* (1964) believe them to be located primarily on arterioles while others e g *Coats* (1912) *Reese* (1956) believe them located on veins

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hyperproteinemia and hyperlipemia (*Kahan Kahan* and *Pintyi* 1964) epilepsy (*Bryson* 1966) hypogammaglobulinemia (*Frenkel* and *Russe* 1967) and as a stage in phacomatosis (*Paufique* 1964)

The purpose of this report is to present a case with the classical signs and symptoms but without there being any evidence of an underlying systemic disease

Case history

A 14 year old boy (chart No 520930) who has been admitted to the department three times at approximately three months intervals the last admission being in October 1967

The 11 year old daughter of the patient s uncle had a congenital cataract (cataracta polaris post dx) but otherwise there was no history of eye disease in the family

The patient had previously been completely healthy

Three weeks before the first admission in March 1967 the patient began to develop symptoms suggestive of a *growing central scotom in the visual field* of the left eye without there being accompanying symptoms

On ocular examination the following findings were noted

Right eye

Vision 1 0 emmetropia

Slitlamp examination ophthalmoscopy biomicroscopy of the fundus gonioscopy tension and perimetry were all normal

Left eye

Vision ability to count fingers only

Slitlamp examination showed normal anterior segment

Ophthalmoscopy including biomicroscopy of the fundus revealed that the papilla was slightly red with a somewhat diffuse nasal and superior border but a sharp temporal border The veins were a little broad and dark red The macular area was edematous and there were yellow hard exudates in a partial star like formation in its upper half

Under the vessels in the periphery of the superior temporal quadrant several whitish yellow slightly raised diffusely defined exudates were seen which were partially confluent centrally The exudates which were primarily located near the equator were surrounded by a broad weakly pigmented area The superior temporal vessels varied markedly in diameter and well defined almost drop like aneurysmal

dilatations were seen on *the finer vessels* both arterioles and veins They were mostly grouped in small clusters but were also present singularly

There were several thin newly formed vessels in the area together with numerous diffusely defined essentially deep hemorrhages but no marked dilatation of the arterioles or veins and no angiomata No direct connections between arterioles and veins were seen There were ensheathing of the veins It was not possible to see the blood column in a whitish degenerated arteriolar branch on ophthalmoscopy with red free light Vascular changes were only localized to the superior temporal vessels particularly the inferior branches Vessels in the other quadrants appeared normal but the veins were somewhat broad and dark red *In addition spread throughout the* posterior fundus especially temporal numerous small well defined yellow white *hard exudates were seen in close relation to the vessels* In several areas the exudates were confluent and surrounded by a broad weakly pigmented area which was most apparent with fundus biomicroscopy

Perimetry revealed a central scotoma of 10 degrees together with a larger defect in the periphery of the lower nasal quadrant Intraocular tension and gonioscopy were normal

With intravenous *fluorescense angiography* (interval 1.5 sec) the following was observed There was no peripheral filling of the superior temporal artery in the area where the aneurysms were seen This was the same vessel where it was impossible to see the blood column with *ophthalmoscopy*

The aneurysms filled slowly and three seconds after filling of the central aneurysms a fine laminary flow could be seen in the vein that lay just below them This flow was seen to be more pronounced in the following pictures No fluorescense could be seen in the most peripheral aneurysms A delicate diffuse exudation of the fluorescein was seen in the area of the aneurysms at 15 seconds which became more pronounced later General physical and neurologic examination revealed no abnormalities in particular no telangiectasis of the skin or buccal mucosa was seen and there was no evidence of pseudoxanthoma elasticum

Bodyweight 59.5 kg Height 1?9 cm Blood pressure 110/ 0 mm Hg Otorhinolaryngologic examination with audiometry and calorimetry was within normal limits The electrocardiogram was normal X ray examination of the skull showed an increased density at the base of the frontal sinus apparently an osteoma but was otherwise normal

Angiographic examination of the left common carotid artery under general anesthesia revealed no abnormalities in particular there were no aneurysms

Laboratory examinations Three hour glucose tolerance test was normal as were the hemoglobin level sedimentation rate MCV MCHC and the leucocyte thrombocyte and differential counts The *serum urea was 95 mg%* and the serum creatinine *was 0.6* mg The total serum protein was 7.1 to 4 gm% Serum protein electrophoresis and immunoelectrophoresis revealed normal immunoglobulin *fractions without* violence of paraprotein Sia's test was negative and there was no cryoglobulin.

The following were within normal limits total lipids (?00 mg%) phospholipids (? 0 mg) total cholesterol (1?3 mg) and neutral fat (1 0 mg%)

There was neither glucose nor protein in the urine and electrophoresis of the urine showed nothing abnormal

The Wassermann and toxoplasmosis reactions were negative

Histologic examination of a skin biopsy taken from the area of the left thigh was

Fig 1

Lebers Retinal Degeneration with Miliary Aneurysms on a 14 years old boy



Fig 2

Photograph of the retina following the intravenous injections of fluorescein Note that there was no peripheral filling of the superior temporal artery corresponding with the ophthalmoscopic picture where the artery in this part was converted into a solid white strand

interpreted as being normal and there were no changes suggestive of pseudoxanthoma elasticum in elastinstained preparations

Discussion

Fluorescense angiography showed reduced flow through the central and no flow through the peripheral aneurysms The prolonged laminar flow through the adjacent veins also suggest a partial block in venous drainage from the aneurysma area

The present study could not give an answer to the question regarding the venous or arterial character of aneurysmal vessel dilatations apart from the dilatations lie between the smaller arteriolar and venous branches

The fluorescein angiographic studies seem to indicate that the aneurysms developed from arteriovenous vessels of foetal character This conception is supported by the studies of e g *Junius* (1934) *Reese* (1956) and *Tour* (1957) who have all considered the primary cause of Leber s disorder to be a con genital telangiectasia

The idea that there is a relationship between the retinal changes and changes in the blood was first suggested by Coats in 1908 and again in 1912 Such a relationship however has only been demonstrated in adults but not in children Thus Woods and Duke in 1963 found hypercholesterolemia in a group of adults with Coats disease but not in a group of 18 children aged from 9 months to 12 years

Of the three patients with Leber s retinopathy mentioned by Kahan in 1964 only two a man of 41 and a woman of 46 years had dysproteinemia (hyper proteinemia with an increased concentration of globulins or specific globulin fractions) and hyperlipemia with hypercholesterolemia The changes in blood were however slight By contrast the third patient a boy of 18 years did not have pathologic changes in serum proteins or serum lipids As the first two patients had in addition skin changes corresponding to pseudoxanthoma elasticum it seems appropriate to consider the retinal aneurysms as having been a part of that generalized condition

Frenkel is the only investigator who has reported retinal aneurysms in a child in connection with changes in the blood chemistry In 1967 he published a case of bilateral retinal aneurysms in a boy of 13 years with congenital hypo gammaglobulinemia together with a similar case of unilateral retinal changes in a 10 years old sister with normal immunoglobulins Frenkel concluded that the changes were the result of a chromosome defect with only partial penetra tion in the sister and that the retinal telangiectasis was the expression of a

mesenchymal defect where the immunoglobulinopathy was only an accompanying secondary change

In the present case the concentrations of the different serum lipids were normal there was no specific increase in the γ-M globulins and the pattern of serum proteins showed no changes from the normal (Prof Rud Keiding M D Central Laboratory Arhus)

Summary

A typical case of Leber s retinal degeneration with miliary aneurysms is described in a 14 year old boy It was not possible to demonstrate abnormalities on the blood in particular there were no pathologic changes in the serum proteins or lipids Fluorescein angiography did not show whether the aneurysms were arterial or venous but did suggest that the arterio venous vessels were of foetal character

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DISTRIBUTION OF TRITIATED BENZYLPENICILLIN IN THE RABBIT EYE

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Introduction

The poor penetration of penicillin into the eye is well known. In anir human experiments bacteriosidic penicillin concentrations have been strated in the aqueous humor after large parenteral doses whereas consi lower concentrations have been observed in the vitreous humor (*Saub* 1956 *Papapanos et al* 1961) *von Sallman et al* (1944) found in rabbits dose of 33 000 IU/kg of intramuscular sodium penicillin a concentratio IU ml in the aqueous humor Concentration in the plasmoid aqueous hu 4 3 I Uml the maximal blood level was 28 IU/ml About similar val reported by *Fritchel* and *Papapanos* (1961) after a dose of 100 00(*Leopold* (1945) followed the intravitreal penetration of penicillin in rabbit eyes and in eyes with infection of the anterior chamber Afte of 4000 IU kg of parenterally given sodium penicillin the concentrati in the vitreous humor from 0 03 to 0 0 IU/ml in the infected eyes No lin was found in the vitreous humor of the noninfected eyes *Sor Ungarn* (1945) demonstrated benzylpenicillin concentrations of 4 to in the aqueous as well as in the vitreous humor of the rabbit after muscular injection of 1 000 000 IU *Hummelt* (1954) used penicillin found in a series of two rabbits a significant rise in the penicillin conc

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of the plasmoid aqueous humor and the aqueous humor of the infected eye *Ullberg* (1954) has examined by autoradiography the distribution of penicillin into different tissues of the rat In the vitreous humor he was able to detect a radioactivity similar to that found in the brain after parenteral administration of benzylpenicillin S^{35}, while the aqueous humor had a slightly higher activity The conjunctiva and the sclera with chorioidea were fairly rich in penicillin

Labelled benzylpenicillin has made possible the examination of the drug distribution in small, separate tissue compartments It lends itself also to an easy analysis of samples from infected material The purpose of the current work has been to investigate the distribution of benzylpenicillin in the different tissues of the rabbit eye and to compare the concentrations reached in the healthy and bacterially infected eye

Material and Methods

Animals 27 rabbits of diverse sexes weighing 2 5 kg were used as test animals

Induction of infection One eye of each rabbit was infected by sticking *Staphylococcus aureus* (penicillin sensitive strain ATCC 6538P) with a thin needle under local Novesin® anesthesia into the vitreous humor through the sclera Vitreous abscess or panophthalmitis developed in all infected eyes during 24 hours

Penicillin injection Benzylpenicillin T potassium [potassium 6 (phenyl acetamido T(G)) penicillinate specific activity 274 mc/mM The Radiochemical Centre Amersham England] and nonradioactive potassium benzylpenicillin (Biochemie Gesellschaft m b H Werk Kundl Tirol Austria) were used 25 rabbits were injected subcutaneously with 2 5 ml of an aqueous solution containing 250 000 IU benzylpenicillin and an amount of 0 1 mC of the labelled material 1000 dpm (disintegrations per minute) equals thus to 1 13 IU Penicillin was injected 24 hours after induction of the infection Two rabbits served as controls and were not injected with penicillin

Preparation and counting of samples The rabbits were killed with intravenously given Nembutal® 0 5 1 2 4 and 6 hours after the penicillin injection five animals in each group Both eyes were immediately enucleated and further dissected taking the aqueous humor cornea iris lens vitreous humor and a triangular piece of the sclera with chorioidea The retina was lost Immediately after death samples were also taken from the heart blood renal cortex liver lung and brain The specimens were weighed in counting vials (the sample size varied from 40 to 500 mg) and digested with 0 2 ml of 60 % percloric acid

and 0 4 ml of 30 % hydrogen peroxide at 80 °C for 2 hours (*Mahin* and *Lofberg* 1966) Thereafter a solution containing 6 4 ml ethylene glycol monoethyl ether 8 6 ml toluol with 6 g/l of PPO and 0 6 g thixotropic gel powder (Cab O Sil Packard Instrument GmbH Frankfurt am Main Germany) was added Counting was performed with a Packard Tri Carb model 3375 liquid scintillation spectrometer External standardization was used for calculating the results in dpm Counts from the tissues of the control animals were used as background values

Statistics Student s *t* test was used in comparing the noninfected eyes with the infected ones

Results

Figs 1 and 2 show the penicillin concentrations in different tissues except the renal cortex during six hours after the injection of the drug The results

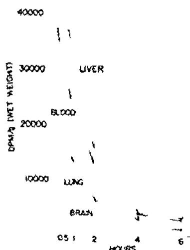


Fig 1

Concentration of benzylpenicillin in the rabbit liver blood lung and brain during six hours after a subcutaneous injection of 100 000 IU kg (0 04 mCi/kg or 89 10⁶ dpm kg) of tritiated benzylpenicillin 1000 dpm equals to 1 13 IU Each point is the mean value of five rabbits vertical bars are standard errors of values

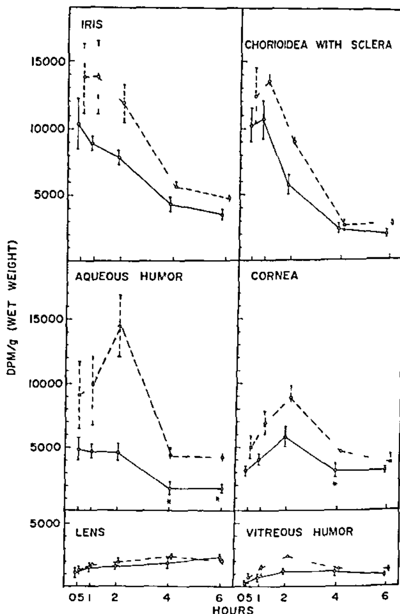


Fig 2

Concentration of benzylpenicillin in different parts of the noninfected (solid line) and bacterially infected (broken line) eyes of the same rabbits as in Fig 1 Each point is the mean value of five (in a few cases four) eyes vertical bars are standard errors of values Asterisks refer to the level of significance when the noninfected and infected eyes are compared *** $P < 0\,001$ ** $P < 0\,01$ and * $P < 0\,05$

are expressed in dpm because both the biologically active penicillin and its metabolites have been counted The inactive penicillin appears however in insignificant amounts (*Kraushaar* 1962 *Ullberg* 1954) the counted metabolites

can thus be ignored Results from the renal cortex revealed values 2.5 to 7 times higher than the corresponding blood level

Discussion

The present results show that penicillin concentration of all tissues in the bacterially infected eye is higher than in the noninfected eye with the exception of the lens The highest values in the noninfected eye are found in the iris and the chorioidea with sclera The aqueous humor and cornea are intermediate and concentrations in the lens and the vitreous humor are during the whole observation period considerably lower than in other ocular tissues The drug levels in the lens and the vitreous are equal to those found in the brain and are about one fifteenth of the maximal blood level

Differences are found also in the timing of the penicillin maximum The concentrations in the vascularized iris and the chorioidea sclera reach their maximum in the infected and noninfected eye shortly after the injection in 0 [illegible] to 1 hour In the aqueous humor of the noninfected eye penicillin achieves the maximal concentration also in half an hour remaining at the same level for two hours In the cornea the maximal concentration is reached first after [illegible] hours since the drug enters the avascularized cornea by diffusion Accordingly penicillin penetrates into the lens by diffusion and has its maximum after 4 to 6 hours Penicillin reaches the vitreous body through the aqueous humor in the posterior chamber the choriocapillaries and the retinal blood vessels and has the maximal level after 2 to 4 hours

Differences in the penicillin concentration between the vascularized parts of the infected and noninfected eye can be explained by the hyperemia caused by the infection The same is true as far as the cornea is concerned where hyperemia in the limbal vascular plexus together with a greater concentration in the aqueous humor leads to an increased penicillin level On the other hand mere hyperemia is not sufficient to account for the three fold concentration difference in the aqueous humor between the noninfected and infected eyes there must also be a change in the tissue permeability A decrease in the outflow is not likely because of the rapid decline of the penicillin level after the maximum One can rather conclude that the increased protein concentration in the aqueous humor of the infected eye (*Peret* and *Tomosi* 1961 *Schumacher* [illegible]) plays a role Thus the great penicillin concentration in the aqueous humor may primarily be due to the easy penetration of protein bound penicillin since about 50 per cent of serum benzylpenicillin is protein bound (*Langham* 1951 *Scholtan* and *Schmid* 1963)

*The growth of penicillin sensitive micro organisms is inhibited by concentrations below 0 5 IU/g corresponding to the values below 500 dpm/g in the present series Concentrations above this limit were observed in all tissues studied Hence the penicillin dosage used, 100 000 IU/kg can be considered sufficient to obtain a therapeutic level in all parts of the rabbit eye

Summary

Distribution of tritiated benzylpenicillin has been investigated in the healthy and bacterially infected rabbit eye The iris and the chorioidea with sclera had the greatest concentrations corresponding to about one third of the maximal blood level Concentrations in the aqueous humor and the cornea were the next and those in the lens and the vitreous humor were equal to those found in the brain being about one fifteenth of the maximal blood level The infected eye had higher concentrations than the healthy one in the iris chorioidea with sclera aqueous humor cornea and vitreous humor but not in the lens The promoting effect of infection on the penicillin penetration was most pronounced in the aqueous humor The dosage used 100 000 IU/kg was considered sufficient to obtain a therapeutic level in all parts of the rabbit eye

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INTRAOCULAR PRESSURE AND EXCRETION OF MUCOPOLYSACCHARIDES IN OSTEOGENESIS IMPERFECTA

BY

LENNART BERGGREN ERLAND WESSLER and JAN WENNERSTRÖM

Osteogenesis imperfecta is as a rule a genetic disease with autosomal dominance It is characterized by fragility of the bones blue sclerae and impaired hearing Different types of the condition can be distinguished These different types should be regarded as different degrees of severity of the same disease rather than as distinct disease entities Although the degree of severity within any one family generally shows only small variations it can vary greatly from family to family Sporadic cases are probbaly mutations Familial and sporadic cases show no significant differences with respect to clinical symptoms and signs No factor connected with the occurrence of mutations is known Plasma calcium phosphorus and alkaline phosphatases are normal Osteogenesis imperfecta is a disorder of the mesodermal tissues with a deficiency in collagen maturation The basic chemical defect is unknown Slightly increased urinary excretion of acid mucopolysaccharides has been reported[6 10]

Ocular manifestations The blue sclerae are not due to a coloration of the sclera itself but to an increased translucency allowing the underlying uveal pigment to become visible Clear sclerae instead of blue sclerae has been suggested as a more exact term The anatomical cause of the transparency has been the subject of dispute Thin fibrous coats may be found but the condition is essentially a persistence of the fetal condition There is a reduction of collagen and a persistence of the precollagenous reticulin as well as an increase in the mucopolysaccharide ground substance indicating an immature fibrous tissue[8] An arcus corneae may be associated with blue sclerae Among other

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more rarely found defects in the eye are keratoconus and cataract of the zonular or cortical type In three cases where glaucoma was present it was of a different type in all of them i e congenital secondary and wide angle respectively Pressure evaluations are lacking Recent reviews of osteogenesis imperfecta have been given by *Smars* (1961)[6] and *McKusick* (1966)[7]

In the present paper an account is given of ophthalmological examinations in 5 cases of osteogenesis imperfecta Pressure determinations and evaluations were of primary interest In order to establish whether the condition is associated with an abnormal mucopolysaccharide metabolism the urine mucopolysaccharide content was also determined

Methods

The ophthalmological examination included subjective determination of the refraction measurement of corneal astigmatism with the Javal Schiotz ophthalmometer slit lamp microscopy and fundus examination Tonometry was performed with the Goldmann applanation tonometer in the sitting position and with a standardized Schiotz tonometer in the supine position The Mueller electronic tonometer was used for tonography

The mucopolysaccharide content of the urine was determined by two methods In the first method (DiFerrante and Rich[5] slightly modified) the mucopolysaccharides were precipitated with cetylpyridinium chloride (CI C) from the non dialyzed urine and the amount of uronic acid in the precipitate was determined In the second method[11] the mucopolysaccharides in dialyzed urine samples were purified on an anion exchanger (Ecteola cellulose) The non sulfated and the sulfated mucopolysaccharides were then eluted with 0 05 M HCl and 5 M NaCl respectively The uronic acid content of the first fraction and the uronic acid and neutral sugar content of the second fraction were then measured The amount of mucopolysaccharides excreted was expressed as mg of uronic acid (hyaluronic acid chondroitin heparitin sulfate chondroitin sulfate) and mg of neutral sugar (keratosulfate) per 24 hours

The accuracy of the collections was checked by creatinine determinations

Case Reports and Results

Case 1 B W A 5 year old man who had a history of 35 fractures up to 16 years of age Blue sclerae were noted already at birth No other cases in the family are

known He has a deformity of the left elbow Hearing is not impaired He also suffers from aortic valvular heart disease

Eye examination Corneae with a peripheral arcus in both eyes Blue sclerae Lens, vitreous and fundus nothing abnormal Both eyes were myopic (about 6 D) With correction the visual acuity was normal The intraocular pressure was around 10 mm Hg in both eyes determined with applanation (R E 10 mm Hg L E 10 mm Hg) and Schiotz tonometry (R E 8 5/5 5 L E 8 0/5 5) The facility of outflow determined by tonography was C R E = 0 24 and C L E = 0 17

The mucopolysaccharide excretion was normal

Case 2 R G A 47 year old woman who had a history of 3 fractures the last one 10 years ago There are several cases in the family (see below) There were no bone deformities and hearing was not impaired

Eye examination Corneae with a peripheral arcus in both eyes Blue sclerae Lens vitreous and fundus nothing abnormal There was no refractive error and the visual acuity was normal *The intraocular pressure was around 10 mm Hg in both eyes* determined with applanation (R E 11 mm Hg L E 10 mm Hg) and Schiotz tonometry (R E 7 5/5 5 L E 8 0/5 5) The facility of outflow determined by tonography was C R E = 0 39 and C L E = 0 27

The urinary muscopolysaccharide excretion was normal as determined after precipitation with cetylpyridinium chloride but slightly increased when determined after purification on Ecteola cellulose

Case 3 E B A 42 year old woman (sister of case 2 R G) She has had 9 fractures the last one at 21 years of age There were no bone deformities and hearing was not impaired

Eye examination Corneae with a peripheral arcus in both eyes Blue sclerae Lens vitreous and fundus nothing abnormal There was no refractive error and the visual acuity was normal The intraocular pressure was around 10 mm Hg in both eyes determined with applanation (R E 10 mm Hg L E 10 mm Hg) and Schiotz tonometry (R E 8 0/5 5 L E 8 0/5 5) The facility of outflow determined by tonography was C R E = 0 23 and C L E = 0 23

The mucopolysaccharide excretion was normal

Case 4 H B A 14 year old boy (son of case 3 E B) He has suffered from 6 fractures There were no bone deformities and hearing was not impaired

Eye examination Corneae nothing abnormal Blue sclerae Lens vitreous and fundus nothing abnormal There was no refractive error and the visual acuity was normal *The intraocular pressure was around 14 mm Hg in both eyes determined* with applanation (R E 13 mm Hg L E 16 mm Hg) and Schiotz tonometry (R E 7 0/5 5 L E 6 0 5 5) The facility of outflow determined by tonography was C R E = 0 37 and C L E = 0 42

The mucopolysaccharide excretion was within normal limits

Case 5 B B A 22 year old woman who developed the tendency to fractures at 9 months of age She had 20 fractures up to 18 years of age but none in the last 4 years There were no bone deformities and hearing was not impaired She has a marked tendency to bruises There are no other family cases and the patient is considered as a mutant

Eye examination Corneae nothing abnormal Blue sclerae Lens vitreous and fundus nothing abnormal Both eyes were myopic and astigmatic (about 3 D) With correction, the visual acuity was normal Repeated intraocular pressure determinations gave low values *i e* around 10 mm Hg in both eyes determined with applanation (R E 10 mm Hg L E 10 mm Hg) and Schiotz tonometry (R E 8 0/5 5 L E

10.5) The facility of outflow determined by tonography was C R. E. = 0.36 and C L. E. = 0.[illegible]6. Pressure determinations with applanation every 5 min during one hour after pilocarpine instillation (2 drops of a 4 per cent solution) in one eye gave a pressure decrease from an initial 10 mm Hg to [illegible] mm Hg. The fellow eye had a constant pressure of 9–10 mm Hg.

The mucopolysaccharide excretion was normal.

The principal results in the 5 cases are summarized in Tables I and II.

Discussion

Common to all the presented cases was low intraocular pressure with applanation and Schiotz values in good agreement indicating normal scleral rigidity. The numeric values from tonography must be interpreted cautiously in view of the initial low pressure level. Furthermore the episcleral venous pressure and its possible variations in osteogenesis imperfecta is unknown and it might be erroneous to assume that it agrees with normal conditions. An episcleral venous pressure of 10 mm Hg must anyhow constitute an upper limit value. However, it appears reasonable to assume that in a connective tissue disorder

Table I

Eye Examinations in Osteogenesis Imperfecta

Case		Arcus corneae	Blue sclerae	Schiotz mm Hg	Applanation mm Hg	Tonography
B. W.	Right Eye	+	+	9.4	10	0.24
	Left Eye	+	+	10.[illegible]	10	0.1
R. C.	Right Eye	+	+	11.[illegible]	11	0.39
	Left Eye	+	+	10.[illegible]	10	0.27
E. B.	Right Eye	+	+	10.2	10	0.[illegible]3
	Left Eye	+	+	10.[illegible]	10	0.23
H. B.	Right Eye		+	1[illegible].[illegible]	13	0.3
	Left Eye		−	14.6	16	0.42
B. B.	Right Eye		+	10.[illegible]	10	0.36
	Left Eye		+	10.2	10	0.26
	Mean			10.9	11	0.29

Table II

Urinary Excretion of acid Mucopolysaccharides (mg/24 h) in Osteogenesis Imperfecta

Case	CPC precipitated	Ecteola purified			
		0 05 M HCl	3 M NaCl		Total uronic acid
	Uronic acid	Uronic acid	Uronic acid	Neutral sugar	
B W	5 8	1 6	4 6	3 4	6 2
R G	2 4	3 0	5 1	3 2	8 0
E B	3 0	1 3	2 9	2 1	4 [illegible]
H B	4 4	1 2	3 9	2 6	5 0
B B	3 9	0 6	2 5	2 0	3 1
Normal limits (ref 5 11)	2 7–7 3	0 7–2 1	2 3–5 2	2 1–3 3	3 1–4 2

such as osteogenesis imperfecta the low intraocular pressure is due to a high facility of outflow

A rough estimation of the corneal thickness in slit lamp microscopy did not in any case reveal an abnormal thinness

Patient B B suffered from a tendency to large bruises even after very slight injuries Another indication of this tendency of spreading in an altered connective tissue was the accidental finding that in the pilocarpine experiment she required new instillations of the local anesthetic every 5 min This was in contrast to a control group of three healthy females of the same age in whom an instillation every 30 min was sufficient

It seems that a condition with less dense fibrous coats than normally allows a better escape of aqueous Does the outflow occur via conventional or unconventional routes? Bill[1] could show that in monkeys (but not in cats) a considerable part of the aqueous passes out of the eye via unconventional uveoscleral routes In cannulated monkey eyes intracameral pilocarpine blocked this route of exit resulting in a pressure increase of a few mm Hg[3]

If there is an unconventional route of exit in the human eye it might hypothetically constitute a comparatively large part of the outflow in this particular connective tissue disorder In case B B repeated applanation tonometry after pilocarpine instillation did not reveal any pressure increase The control group behaved similarly It was thus not possible with this rough method to prove the existence of unconventional routes of exit in the living intact human eye

The clinical pictures of hereditary disorders of connective tissue are well established but information on the fundamental defects is still scanty Dominant disorders generally suggest a change in a structural protein and recessive disorders inborn errors of metabolism[7] In the different types of mucopolysaccharidoses considerable urinary excretion of acid mucopolysaccharides is characteristic In recent reports of osteogenesis imperfecta[9, 10] some cases showed a slightly increased excretion In the present investigation the mucopolysaccharide excretion was quantitatively and qualitatively normal in four cases and slightly increased in one An increased mucopolysaccharide excretion due to a slightly altered mucopolysaccharide metabolism however might be a nonspecific response occurring in a variety of diseases[4] A disorder of the ground substance of such a type as in the mucopolysaccharidoses is unlikely

Summary

The eyes of five patients with osteogenesis imperfecta were clinically examined All had blue sclerae and three of them had an arcus corneae There were hereditary as well as sporadic cases in the material and the age ranged from 14 4 years The syndrome seems to be combined with a low intraocular pressure which could be explained by a high facility of outflow The scleral rigidity was normal The routes of exit are discussed The urinary excretion of acid mucopolysaccharides was quantitatively and qualitatively normal in four cases and slightly increased in one

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MUCUS FLOW IN THE CONJUNCTIVA

Rate of Migration of the Mucous Thread in the Inferior Conjunctival Fornix towards the Inner Canthus

BY

M S NORN

It is a well known fact that the mucus of the nasal mucosa moves across the epithelium towards the pharynx thereby cleansing the mucous membrane This mucus flow is due to the cilia of the epithelial cells

The flow rate of mucus in the nose or trachea has been measured in an operation microscope in which the mobility of charcoal particles (*Dalhamn*) or dyed particles (*Ewert*) in the mucus can be observed The measurement is difficult because particles within the same area may pass at different rates even if equal in size

The mucus is secreted by goblet cells The topography of the goblet cells in the *conjunctiva* was described recently by *Kessing*

The goblet cells contain mucous granules These granules are homogeneous presenting no structure whatever not even when examined in an electron microscope

In contrast to these the mucus in the conjunctival fluid is arranged in fibrils

Using Giemsa's or Papanicolaou's staining method for instance the goblet cell contents are stained differently from the conjunctival mucus (*Norn* 1963 A) The mucus must therefore be supposed to be present in the form of a precursor inside the goblet cell

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The mucus is excreted through the orifice of the goblet cell It then swells becomes fibrous detaches itself and floats into the conjunctival fluid

The excreted mucus tends to be caught by and adhere to irregularities on the cornea or conjunctiva (erosion ulcer, foreign bodies) Sutures may be enveloped in considerable amounts of mucus

The mucus is at last collected into a long mucous thread in the inferior conjunctival fornix A similar but smaller thread is found in the superior fornix

The mucus in the conjunctival sac and on the cornea can be vital stained with alcian blue The mucus is then seen as dots or more rarely as strands scattered over the conjunctiva and sometimes also over the cornea

The flow rate of the mucus from the moment it leaves the goblet cell until it joins the mucous thread in the inferior conjunctival fornix varies appreciably (from less than 1 minute to more than 30 minutes) Mucous enveloping sutures can stay for hours

The author of the present paper has given the first detailed description of the mucous thread in the inferior conjunctival fornix

It is a well known fact that in keratoconjunctivitis sicca for instance mucous shreds may be found in the inferior fornix *Absolon et al* among others, observed such in 27 out of 30 sicca patients after vital staining with rose bengal

However using mucus specific vital staining with alcian blue I was able to show that the mucous thread in the inferior conjunctival fornix is a constantly present physiological phenomenon It is observable in all normal conjunctivae (fig 1)

In pathological cases the mucous thread may be particularly large (kerato



Fig 1

Mucous thread in the inferior conjunctival fornix vital staining alcian blue

conjunctivitis sicca, aestival conjunctivitis lagophthalmos) or particularly vulnerable (infectious conjunctivitis)

A rudimentary or absent mucous thread has been observed in no more than one pathological state namely in that of pemphigus conjunctivae

In the presence of pemphigus conjunctivae the epithelium becomes irregular keratinized The goblet cells disappear a fact which explains the absence of the mucous thread

In all other pathological states a mucous thread resembling the physiological is present

The mucous thread in the inferior conjunctival fornix consists of long parallel mucous fibrils which seem to consist of acid mucopolysaccharides Cells of different kinds (epithelial cells neutrophilic leucocytes lymphocytes) fibrinous strands foreign bodies and vacuole like formations containing amorphous masses (*Egeberg & Norn Norn* 1966) are found scattered in the mucous thread

The mucous thread in the inferior fornix moves slowly towards the inner canthus where it gradually creeps on to the skin and dries up to become sleepy seeds

To my knowledge no investigations into the flow rate of mucus in the conjunctiva have been published so far

The object of the present investigation was to study this migration of the mucous thread *Why does the mucus migrate?*

The epithelial cells of the conjunctiva have no cilia thus being not responsible for the mucus flow

The investigation was based on a clinical material to clarify whether the flow rate differs in different clinical states

Method

Preliminary examinations were made after introduction of a small number of graphite particles laterally in the inferior conjunctival fornix After the patient had blinked a few times these particles accumulated in the mucous thread and their position was measured The position of the particles was measured again after 10 minutes The migration rate could now be calculated

In few instances the particles were seen not to have moved after 10–30 minutes but in most cases they were transported towards the inner canthus The possibility might be conceived that fairly large particles may adhere to the conjunctival epithelium and thus interfere with the normal flow of the mucous thread

The mucus is excreted through the orifice of the goblet cell It then swells becomes fibrous detaches itself and floats into the conjunctival fluid

The excreted mucus tends to be caught by and adhere to irregularities on the cornea or conjunctiva (erosion ulcer foreign bodies) Sutures may be enveloped in considerable amounts of mucus

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Fig 1

Mucous thread in the inferior conjunctival fornix vital staining alcian blue

Material

A total of 208 eyes from 104 patients were examined These were patients from an ophthalmological practice an ophthalmic out patient department an ophthalmic unit and patients referred for routine examination from other hospital units

The diagnoses are seen in table \

Does the mucus flow at a constant rate?

The mucus flow might be conceived to be uneven e g slow at the outer canthus to increase proximally and reach maximum at the inner canthus If so the mucus flow measured on the basis of an initially long vital stained thread will apparently be slow whereas measurement on the basis of an initially short vital stained thread will give a too rapid flow rate

Table I shows that the mucus flow rate is constant averaging 10 4 mm/10 minutes at least within the area with an initial vital stained mucous thread length of from 6 to 15 mm i e the interval within which 79 per cent of the measurements were made

Where the initial vital stained mucous thread was under 5 mm in length from the punctum lacrimale (11 per cent of the whole material) the flow value seems to have been estimated too low This may be due to the thread tending to wind at the inner canthus before it creeps on to the skin This will check the migration of the thread and the area traversed will be shorter than in the free part of the inferior fornix

The flow could not be assessed in the cases where the mucous thread had crept on to the skin The examination was repeated in some instances with a shorter observation period

With an initial vital stained thread exceeding 16 mm the flow rate was perhaps estimated too high This was so in 9 6 per cent of the material

Table I

I x)le lepen len e of the measure l mucus flow rate on the length of the vital stained muc us thread on first rea ling

l ngth f mucus thread n mm measured from inf punct lacrimal flow in mm 10 m ns)

n t al n u us th ead length	0–5	6–	8–9	10–11	1 –13	14–15	≥ 16
n mu us fl w	0	10 0	9 9	10.5	8 4	11 °	16 °
number f ses	1	31	15	63	[illegible]	31	90

However the results of the preliminary examinations did not differ significantly from those achieved using the present method

In the studies described below I therefore preferred to render visible the normally invisible limpid mucous thread by vital staining with the mucus specific alcian blue

An alcian blue solution is instilled into the conjunctival sac, after which the patient looks upwards, and the lower lid is kept everted for about 15 seconds The dye stains the mucous thread in its entire length together with smaller amounts of mucus in the inferior fornix The position of the mucous thread is measured before and after the observation period

Using this technique the line of junction between alcian blue stained and non stained mucous thread is often indistinct and the measuring point is therefore ill defined

To avoid this disadvantage a technique was chosen staining only half of the mucous thread

The following technique was employed for all the examinations

The patient looks upwards The medial half of the lower lid is everted by one of the examiner s fingers while the lateral half is occluded by another finger which presses the lid against the eyeball

A plastic tube fitted with a cannula to be used only once is employed for instilling, without touching the conjunctiva 0 01 ml of an aqueous 0 25 % alcian blue solution into the open medial half of the inferior conjunctival fornix

The eyelid is kept in this position for about 15 seconds and then released

After another minute or so the lid is everted again and the alcian blue stained part of the mucous thread is measured by measuring the distance from the lower punctum lacrimale to the line between the stained and the non stained thread

In about half of the experiments the measurement was performed in the slit lamp mounted with a measuring eye piece and in the other half grossly by means of a scale

Exactly 10 minutes later a similar measurement was performed using the same technique By this procedure the migration rate of the line of junction between stained and non stained mucous thread could be calculated

Example 1 Distance from punctum lacrimale to distal end of the stained mucous thread is 12 mm at first measurement against 2 mm in the same direction at second measurement 10 minutes later The flow of the mucous thread is thus 10 mm/10 minutes

Example 2 Distance from punctum lacrimale to distal end of the stained mucous thread is 12 mm At second measurement this stained distal end has passed the punctum lacrimale being now situated 2 mm proximal to this The mucus flow is 14 mm 10 minutes

Material

A total of 208 eyes from 104 patients were examined These were patients from an ophthalmological practice an ophthalmic out patient department an ophthalmic unit and patients referred for routine examination from other hospital units

The diagnoses are seen in table X

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Table I

I ssible dependence of the measured mucus flow rate on the length of the vital stained mucous thread on first reading

l ngth f muc us thread n mm measured from inf punct lacrimal flow in mm 10 mins)

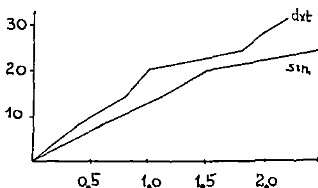
n t al mu us th ea l leng h	0–5	6–	8–9	10–11	12–13	14–15	≧ 16
me n mu us flow	0	10 0	9 9	10.5	[illegible]	11.2	[illegible]
numbe f yes	3	31	18	63	[illegible]	31	[illegible]

Graph I illustrates an experiment carried out on myself The mucus flow rate is seen to have been constant in the main On the other hand it is also seen that the flow may vary somewhat unsystematically Repeated measurements in the same patient gave the same impression

Extrinsic Factors

The moisture of the atmosphere has a great influence on the mucus flow in a ciliated epithelium *Ewert* found an average flow of 4 2 mm/min in the nasal mucosa at 43 6 % moisture but twice the flow rate at 100 % moisture

Table II shows the mucus flow in the conjunctiva to be independent of the moisture of the atmosphere



Graph I

Continuous mucus flow measurement Experiment on myself
Abscissa migration of mucous thread in cm Ordinate time in minutes

Table II

Possible dependence of the conjunctival mucus flow on the moisture of the atmosphere (Moisture measured with hair hygrometer mucus flow in mm/10 mins) A total of 86 eyes mean mucus flow 10 /

moisture	*35–39*	*40–44*	*45–49*	*50–55*
mean mucus flow	10 4	9 5	13 5	12 0
number of eyes	18	44	16	8

The moisture was in all 86 cases measured with the same hair hygrometer. The absolute values are not exact, but the relative variations are reliable.

The flow rate seemed to be independent of the minor *temperature* variations that may occur in the consulting room (table III).

In 24 cases a mydriatic (cyclogyl or epitromine) was *instilled* prior to the mucus flow measurement. The mean flow was 11.3 mm/10 minutes compared with 10.4/10 minutes in the total material (208 eyes). In other words, the preceding instillation had no unquestionable influence on the flow rate.

Tear Secretion

The tear production was measured by a method developed by the author: Lacrimal streak dilution test (*Norn* 1965 A).

0.01 ml of a mixture of 1 % rose bengal and 1 % fluorescein is introduced into the conjunctiva. Exactly 5 minutes later the tint of the lacrimal streak is read in the slit lamp.

An intense red colour indicates that the tear production has been practically *nil* during the observation period.

A weak yellow colour signifies a considerable tear production, the original red colour having been diluted by a considerable amount of tear fluid.

The tint is compared with a series of dye dilutions in capillary glass tubes on the basis of which the tear production can be calculated.

The values in a normal material range between 32 and 1024 times dilution in the course of 5 minutes (*Norn* 1965 B).

The tear secretion was examined in [illegible]9 eyes. The cases were in some measure selected. The tear production was therefore definitely reduced in no less than 11 cases.

Table IV shows the mucus flow rate to be reduced in relation to a diminished tear production and normal in relation to a normal production. The mucus flow thus seems to depend on the tear production, perhaps in the manner that the tear flow presses the mucous thread proximally.

Table III

The dependence of the conjunctival mucus flow on the environmental temperature (86 eyes)

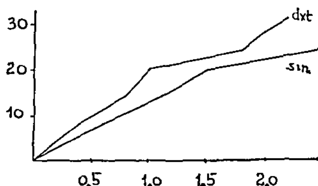
temperature	16–1[illegible]	18–19	20–21
mean mucus flow	9.0	11.1	11.0
number of eyes	[illegible]0	[illegible]0	46

Graph I illustrates an experiment carried out on myself The mucus flow rate is seen to have been constant in the main On the other hand it is also seen that the flow may vary somewhat unsystematically Repeated measurements in the same patient gave the same impression

Extrinsic Factors

The moisture of the atmosphere has a great influence on the mucus flow in a ciliated epithelium *Ewert* found an average flow of 4 2 mm/min in the nasal mucosa at 43 6 % moisture but twice the flow rate at 100 % moisture

Table II shows the mucus flow in the conjunctiva to be independent of the moisture of the atmosphere



Graph I

Continuous mucus flow measurement Experiment on myself
Abscissa migration of mucous thread in cm Ordinate time in minutes

Table II

Possible dependence of the conjunctival mucus flow on the moisture of the atmosphere (Moisture measured with hair hygrometer mucus flow in mm 10 mins) A total of 86 eyes mean mucus flow 10 ,

moisture	35–39	40–44	45–49	50–55
mean mucus flow	10 4	9 5	13 5	12 0
number of eyes	18	44	16	8

Table VI

Dependence of mucus flow on lid strength 202 eyes

	weak	moderate	strong
lid strength	weak	moderate	strong
mean mucus flow	9.9	10.4	11.5
number of eyes	60	94	48

Width of Palbebral Fissure

The width of the palpebral fissue was measured while the patient looked straight ahead

It is seen in table VII that the mucus flow hardly depends on the width of the palpebral fissure though the flow rate seemed to be the highest at a width of about 9 mm whereas slower at narrower or wider fissures

Foam

Foam formation at the outer canthus and along the ciliary margins may be seen in normals and in various pathological states perhaps in increased amounts in cases of exophthalmos and chronic simple conjunctivitis The foam formation depends on the viscosity and surface tension of the conjunctival fluid It is promoted by blinking (Norn 1963 B)

The occurrence of foam was assessed by an arbitrary graduation from 1 to 5

No relationship was demonstrable between the occurrence of foam and the mucus flow rate (table VIII) This goes to show that neither surface tension nor viscosity has any decisive influence on the mucus flow rate

Reproduction of the Mucous Thread

If the mucous thread is removed another one will develop and have reached the same size and shape as the former after 30 minutes

The mucous thread has not yet been fully reproduced after 2–10 minutes

Table VII

[illegible] dependence of the mucus flow on width of palpebral fissure 20[illegible] eyes

width of palpebral fissure	< 8	8	9	10	> 10
mean mucus flow	9	9.4	13.4	11.4	9.3
number of eyes	60	4[illegible]	34	56	30

Table IV

Dependence of the conjunctival mucus flow on tear production
(Tear production estimated by tear streak dilution test /5 mins 29 eyes Red colour corresponds to weakest tear production yellow to maximum tear production)

tear production = colour of tear streak after 5 mins	red	orange	yellow
mean mucus flow	5.6	6.6	10.0
number of eyes	11	8	10

Blinking

The *frequency of blinking* was studied while the patient was observed through the slit lamp in moderate light In most cases the time it took to blink 10 times – more rarely 20 times – was measured by means of a stop watch The frequency was often seen to be highly variable The patient was not instructed in advance of the purpose of the examination

The values set out in table V suggest that the mucus flow rate depends on the blinking Thus frequent blinking (short intervals between two successive blinkings) seemed to accelerate the mucus flow rate A total of 182 eyes were *examined*

The *muscular strength* of the eyelid (orbicularis oculi) was assessed by a digital estimate of the strength while the patient closed the lid gently at first and thereafter maximally (cf *Miller)*

The results were recorded as weak moderate or strong

The muscular strength of the lid seemed to influence the mucus flow rate (table VI) strong lids accelerating the flow and weak lids reducing it

Thus frequent blinking and vigorous blinking seem to promote the mucus flow The differences of the flow values are small however

Table V

Dependence of the mucus flow on frequency of blinking 182 eyes

time interval between two blinkings (seconds)	< 5	5–6	7–8	> 8
number of blinkings per minute (converted)	> 12	12–10	9–8	< 8
mean mucus flow (mm 10 mins)	11.0	10.4	10.1	9.1
number of eyes	82	46	26	28

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Dependence of mucus flow on lid strength 202 eyes

lid strength	weak	moderate	strong
mean mucus flow	9.9	10.4	11.5
number of eyes	60	94	48

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width of palpebral fissure	< 8	8	9	10	> 10
mean mucus flow	9	9.4	13.4	11.4	9.3
number of eyes	60	47	34	36	30

Table IV

Dependence of the conjunctival mucus flow on tear production

(Tear production estimated by tear streak dilution test /5 mins 29 eyes Red colour corresponds to weakest tear production yellow to maximum tear production)

tear production =			
colour of tear streak after 5 mins	red	orange	yellow
mean mucus flow	5 6	6 6	10 0
number of eyes	11	8	10

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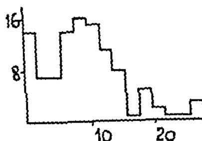
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Table V

Dependence of the mucus flow on frequency of blinking 182 eyes

time interval between two blinkings (seconds)	< 5	5–6	–8	> 8
number of blinkings per minute (converted)	> 12	12–10	9–8	< 8
mean mucus flow (mm 10 mins)	11 0	10 4	10 1	9 1
number of eyes	82	46	26	8



Graph III
Mucus flow rate in 105 pathological eyes
Abscissa mucus flow in mm/10 mins Ordinate number of eyes

noticed (0 mm/10 minutes) In these three cases a flow could be elicited how ever by intensified blinking

No significant sex or age difference was demonstrable with regard to the mucus flow rate (table IX) in contrast to the tear secretion which decreases with increasing age (*Norn* 1965 B)

The mucus flow rate in the conjunctiva is much slower (1 1 mm/min) than that in the nose (4–10 mm/min) The mucus flow in the nose is likewise inde pendent of age and sex (*Ewert*)

Table IX
Mucus flow in normals Age and sex variations 103 eyes

age	mean mucus flow	number of eyes
0–19	14 3	5
0– 9	10 7	
30–39	9 9	1
40–49	[illegible]	14
50–59	10 1	[illegible]
60–69	1 6	21
0– 9	1 1	14
≥ 80	9 0	6
females	10	5
males	17 0	46
Total	11.5	103

Table VIII

Possible dependence of the mucus flow on occurrence of foam along palpebral border especially outer canthus 126 eyes

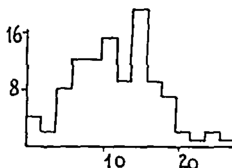
occurrence of foam grade	0	1	2	3	4
mean mucus flow	14 0	10 2	9 6	10 5	13 4
number of eyes	12	44	47	16	7

Staining with alcian blue at this point of time shows a smaller mucous thread the thickest over the area of the middle one third of the inferior fornix and surrounded by flat mucous patchings on the epithelium round the inferior fornix At this stage the thread thus differs from the normal mucous thread which usually is the thickest over the proximal one third and which passes as a continuous thread from the lateral part of the inferior fornix to its proximal part and further right into the inner canthus

Normal Material

A total of 103 normal eyes were examined The mucus flow averaged 11 3 mm/10 minutes i e just over 1 mm/min

The flow may vary considerably as shown in graph II The maximum flow noticed was 26 mm/10 minutes while in three cases no flow whatever was



Graph II

Mucus flow rate in 103 normal eyes

Abscissa mucus flow in mm 10 mins Ordinate number of eyes

In two cases the mucous thread was completely immovable in one also after intensified blinking

The reduced flow seemed to be independent of a possible closing defect (lagophthalmos) and the flow might be reduced even at a normal tear secretion

Entropion – Ectropion

A greatly reduced flow was noticed in three cases of entropion In two the thread was immovable but moved in response to intensified blinking

The mean flow was doubtfully reduced in five cases of ectropion

In one case of ectropion the mucus flow was normal despite arrested tear secretion

In ectropion the tear secretion is reduced or arrested presumably as a compensatory measure to prevent overflow owing to absent lacrimal passage (*Norn* 1966 A)

The greatly reduced flow rate seen in cases of ectropion facial paralysis and keratoconjunctivitis sicca is not due to the above mentioned source of error namely an initially too short vital stained mucous thread

Infectious Conjunctivitis

In bacterial infectious conjunctivitis the mucous thread tends to divide because it is traversed by a stream of neutrophilic leucocytes The mucous thread is often seen to run over on to the lower lid at the middle of this

The mucous thread nevertheless moves towards the inner canthus as in normal eyes The mean mucus flow rate was found to be only doubtfully reduced

Other Pathological States

In cases of *chronic simple conjunctivitis* (i e chronic conjunctival complaints with no objective signs) and *blepharoconjunctivitis* the mucus flow was as in normals

In one case of *pemphigus* conjunctivae with arrested tear secretion the rudimentary mucous thread was immovable also after intensified blinking

A reduced mucus flow was found in one case of soda induced *erosion*

A normal mucus flow was present in cases of *epiphora* and *aestival* conjunctivitis as well as in one patient with congenitally closed *punctum lacrimale* and arrested tear secretion and in one patient with a *prosthesis*

An accelerated mucus flow was observed in a patient with *palpebral fibrillations* and in a person wearing contact lenses who had a greatly increased blinking frequency

Pathological Material

A total of 105 pathological eyes were examined The diagnoses are recorded in table X A mean mucus flow rate of 9.5 mm/10 minutes was measured This was a slower rate than that in the normal material (graph III)

Keratoconjunctivitis Sicca

The mean mucus flow rate was lower than in the normal material (4.2 mm/10 minutes)

The mucous thread was completely immovable in one case even after 25 minutes and after intensified blinking In two cases the mucus flow rate was nearly normal (8 and 9 mm/10 minutes)

The strikingly thick mucous thread in all six cases is characteristic feature of this disease (*Norn* 1963 A)

Facial Paralysis

The mean mucus flow rate was also reduced in this disease being 4.2 mm/10 minutes against 15 mm/10 minutes in the contralateral normal eye

Table X

Mucus flow in normal and different pathological states 208 eyes
(mucus flow in mm/10 mins)

diagnosis	mean mucus flow	number of eyes
normal	11.3	103
infectious conjunctivitis	8.7	15
simple chronic conjunctivitis	11.2	24
chron blepharoconjunctivitis	11.0	6
keratoconjunctivitis sicca	4.2	6
facial paralysis	4.2	5
entropion	2.0	3
ectropion	7.7	6
keratitis corneal erosion	11.7	7
epiphora	8.3	4
exophthalmos	10.3	7
other	11.1	22
total of pathological	9.5	105
total material	10.4	208

In two cases the mucous thread was completely immovable in one also after intensified blinking

The reduced flow seemed to be independent of a possible closing defect (lagophthalmos) and the flow might be reduced even at a normal tear secretion

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An accelerated mucus flow was observed in a patient with *palpebral fibrillation* and in a person wearing contact lenses who had a greatly increased *blinking frequency*

Intensified Blinking

In 25 cases the patient performed intensified maximum blinkings for 2 minutes following measurement of the normal mucus flow through 10 minutes

The mean mucus flow rate was higher after 2 minutes of intensified blinking than after 10 minutes of normal blinking

Local Treatment

Cautious washing of the inferior conjunctival fornix with saline seemed to have no particular accelerating effect on the mucus flow (2 ml of saline in a steady flow in the course of 2 minutes)

Instillation of 0 5 % silver nitrate or the protein hydrolysing alpha chymo trypsin (2 mg/ml) altered the mucous thread

Silver nitrate rendered the thread greyish milky, "clotted After chymo trypsin the mucous thread was liable to break into fragments

The migration rate of this altered mucous thread seemed however to be approximately normal

The mucus flow seemed to remain uninfluenced by alteration of the surface tension of the conjunctival fluid (experiments with methylcellulose vaseline paraffin ointment and silicone ointment (Antifoam A))

Bandage

Bandage to the eye was found to reduce the mucus flow The flow did not cease if the patient could blink under the bandage

Anaesthesia

The mucus flow was completely arrested in states of general anaesthesia (three experiments with up to 45 minutes of observation)

Sleep

In three experiments on myself (both eyes each time) alcian blue was instilled before closing the eyes at night The mucus flow was measured as soon as possible on opening the eyes in the morning after a whole night s sleep

The mucus flow was found to be between 1 and 23 mm (mean flow 10 5 mm in more than 360 minutes i e a scant 1/36 of the normal)

A few short mucous thread fragments were found scattered in the inferior fornix After awakening blinking soon removed these fragments which crept on to the skin at the inner canthus where they dried up to become sleepy seeds

The mucus flow is thus greatly reduced during sleep probably even arrested during profound sleep when presumably neither tear secretion nor blinking takes place The recorded very slow flow is most likely due to blinking immediately before falling asleep or at the moment of beginning awakening

Discussion

The technique employed in the present study for measuring the migration of the mucous thread is subject to rather material sources of error

The mucous thread is vital stained by alcian blue As the dye combines with the mucus it is likely to alter the properties of the mucous thread However the distal half or so of the mucous thread remains unstained and relatively unaffected

The alcian blue solution is fairly acid pH 3 8 (measured in the Central Laboratory *Kommunehospitalet*) and hypo osmotic It is impossible to render it isotonic by adding salts glucose or sodium hydroxide because addition of these substances causes alcian blue to precipitate The conjunctival environment is altered by adding alcian blue

The mucous thread is normally invisible limpid It is therefore impossible to measure the mucus flow without somehow or other disturbing the original environment

Addition of graphite particles involves other sources of error However exploratory experiments gave mucus flows of the same order as experiments with alcian blue stained mucous threads

The mucus flow may vary considerably as is evident for instance from continued flow measurement in the same subject (graph I) or from the distribution of the normal material (graph II) The great fluctuations may be due among other things to varying frequencies and intensities of blinking

Causes of Mucus Flow

The mucus flow rate might be conceived to depend on blinking tear secretion r the viscosity of the mucous thread and its adhesion to the foundation

The two factors adhesion and viscosity seemed to be of no importance wherea both blinking and tear secretion were found to have a certain influence

In the inferior fornix the flood of tears moves from the outer canthus towards the punctum lacrimale This can explain the movement of the mucous thread from the outer canthus towards the inferior punctum but not its further

movement proximally from the punctum lacrimale on to the skin at the inner canthus

The results of the clinical and experimental studies suggest that a reduced flood of tears inhibits the mucus flow (keratoconjunctivitis sicca facial paralysis sleep anaesthesia) On the other hand cases were occasionally found in which the mucus flow was normal, despite a reduced flood of tears

A diminished tear secretion is often found co incidently with a reduced function of the lid muscles of the "tear pump (facial paralysis sleep anaesthesia) It is therefore difficult to decide whether in such cases a slower flow is due to a reduced muscular function or to a reduced flood of tears

The movements of the lid muscles must have a great influence on the mucus flow This is evidenced by the fact that intensified blinking greatly accelerates the mucus flow rate while, on the other hand, a pronounced paralysis slows down the flow

The mucous thread seems so to speak to be "kneaded forwards along the bottom of the inferior fornix between the two conjunctival laminae

Size of Mucous Thread

In a previous study I found the mucous thread to be particularly large in relation to keratoconjunctivitis sicca aestival conjunctivitis and lagophthalmos (*Norn* 1963 A)

This might be due to a very slow mucus flow with a consequent accumulation of much mucus in these conditions

The present study showed in fact that the mucus flow rate may be greatly reduced in cases of keratoconjunctivitis sicca and facial paralysis

On the other hand some such cases have been met with in which the mucous thread was large while at the same time the flow was normal The increased amount of mucus must therefore be due in part at least to an increased production in these conditions

In pemphigus conjunctivae the mucus flow and also the amount of mucus were found to be reduced The amount of mucus produced must here be very small

No clinical condition seems to be characterized by an increased mucus flow This has only been seen in solitary cases (palpebral fibrillations frequently blinking wearers of contact lenses)

Natural Cleansing of Conjunctiva

Foreign bodies of different kinds (hair dust threads etc) are caught by the conjunctival mucus and end in the mucous thread (*Norn* to be published)

The migration of the mucous thread must therefore play a decisive role

in the cleansing of the conjunctiva A slowed down flow involves impairment of the natural cleansing This is so under a bandage as well as during general anaesthesia and sleep

In keratoconjunctivitis sicca facial paralysis and entropion the risk of contamination must be expected to be greater than in conditions with a normal mucus flow The risk will be further increased if the tear secretion is low

Williamson et al showed in agreement with this that the conjunctiva contains more fungi in patients with keratoconjunctivitis sicca than in normals

Summary

The conjunctival mucus accumulates to form a mucous thread in the inferior conjunctival fornix The mucous thread is always present also in normal eyes It moves towards the inner canthus where it creeps on to the skin to form sleepy seeds

The rate of this mucus flow has been studied in 208 eyes after vital staining with 0 25% alcian blue

In normals the mean flow rate was found to be 1 1 mm/min independent of age sex environmental temperature and moisture

The rate was seen to be reduced in cases of facial paralysis entropion keratoconjunctivitis sicca and pemphigus conjunctivae while doubtfully so in infectious conjunctivitis

A normal rate was observed in patients with chronic simple conjunctivitis and blepharoconjunctivitis

The mucus flow rate is reduced in response to weak or infrequent blinking and in cases of diminished tear production The mucus flow is arrested during anaesthesia and sleep

Intensified blinking raises the mucus flow rate

The conjunctival mucus flow is a factor of importance in the natural cleansing of the conjunctiva

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From the Eye Clinic The National Institute for the Blind and Partially Sighted Copenhagen (Head H Skydsgaard M D)

OPHTHALMOLOGIC AND ORTHOPTIC EXAMINATIONS OF DYSLECTICS

BY

M S NORN EVA RINDZIUNSKI) AND H SKYDSGAARD

Specific reading difficulties in school children and also in adults have during the past more than 30 years been a problem of increasing topical interest and far reaching social importance

Reading deficiency is a *condition* covering the domains of educationists psychologists and physicians alike It is a defect on the borderline *between* purely medical disciplines on one hand and clinical experimental *psychology* and educational problems on the other

Since the first publications in this country by *Orum* and *Ronne* the question has been dealt with in numerous papers by physicians psychologists and *educationists on different* bases and from widely different points of view *The international* literature now available on the condition is immense The questions of its terminology delimitation *and not the least* important fundamental character *i e the nature of* the functional disorder and its aetiology and genesis have in the course of time been subjects for *discussion*

It was soon found difficult to *define the concept of* congenital word blindness because in its mild forms it is almost clinically indistinguishable from physiological *variants (the* normal slow readers) and not infrequently it is veiled by exogenous factors *(see below)*

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in normally and highly gifted children as a syndrome characterized by typical difficulties of reading writing and spelling occasionally in association with difficulties of interpreting other symbols (figures musical notes Morse system shorthand writing) The condition is not infrequently accompanied by defects of various non linguistic functions referable to a dysfunction of the parietal lobes or the parieto occipital zone Such defects are characterized mainly by a failing sense of space right left confusion uncertain sense of form constructive apraxia manifesting itself among other things by dyslexia dysgraphia and similar agnostic apractic symptoms In more severe cases the condition is complicated by impressive and expressive defects of the linguistic development According to K *Herman* who has performed thorough comparative analyses of Gerstmann s syndrome*) and congenital word blindness all the stated categories of symptoms are referable to a defect of the directional function and it is presumably this defect which is transmitted by dominant inheritance to word blind families We must thus accept congenital word blindness not only as a *nosographic* but according to *Hermann* probably also *nosologic* entity *Hermann s* proposition must be regarded as the best substantiated theory advanced so far of the existence of a specific basic disorder a morbid factor so to speak In our days when word blindness (in Denmark) is included under the system of public care a diagnostic differentiations is simply called for

To use nowadays the term congenital word blindness and its synonyms for any form of reading difficulty would give rise to renewed obscuration and confusion

The necessity of this differentiation has been emphasized by several writers (*Hallgren Nicholls Goldberg* and others) *Goldberg* writes There is a strong presumptive envidence that the cases of primary reading retardation are associated with a lesion in the parietal occipital lobe

Clinically we must of course reckon with mixed types where exogenous factors of the stated kinds may conceal or accentuate a genuine predisposition to word blindness whose nature it may be difficult to verify at first This may not be possible till after a long observation time with elimination of possible exogenous factors

It is beyond the scope of the present paper to enter on a full assessment of the condition or to give an approximately satisfactory description of the polymorphous clinical picture especially of the qualitative reading and writing deficiencies As stated in the introduction such would also require a team work in its widest sense by specialists within psychology education and medicine (*Park* a group of experts)

When dealing with congenital word blindness we aimed merely as the title

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* ght left confusi n finger agnosia acalculia agraphia

From non medical quarters a tendency was noticed towards regarding all reading difficulties merely as different degrees of the same defect with smooth transitions from the normal reader to the illiterate Adherents to this view were disinclined to accept any form of specificity, while at the same time they were opposed to the term word blindness

Therefore attention was focused on various external or peripheral links of a chain of suspected causes at the expense of a more profound analysis of the psychosomatic functions determining the course or development of the reading process itself *Knud Herman* recently discussed these problems in detail in his monograph *Medfodt Ordblindhed* (Congenital Word Blindness)

It is impossible in this paper to deal extensively with the problem from a diagnostic and a symptomatologic aspect

However, a rational evaluation of this problem requires also where such *a short presentation is concerned that among the* numerous children with reading difficulties those with congenital word blindness are singled out in a separate group with genetic symptomatologic and prognostic characteristics This procedure has from the very beginning been advocated within medical circles

The reading retardation the delayed or deficient reading ability is no more than the unspecific symptom common to the whole group

The final distinction is based on the psychomechanical complications underlying the symptom in cases of congenital word blindness (dyslexia) In such cases it is the very act of reading the symbol interpreting function which cannot be accomplished despite optimum somatic, mental and social conditions It is the difference between seeing and interpreting the symbols

We must distinguish between the *primary reading retardation* (proper reading difficulties *for which the medical term is congenital word blindness* or constitutional specific dyslexia) and the *secondary reading difficulties* (constituting by far the largest group)

The *secondary reading difficulties* are symptoms of *intelligence defects brain damages* and a great number of *exogenous factors* which separately or collectively obstruct the development of a normal reading ability at the normal time in spite of an intact cerebral activity including the intellect *Mental peculiarities* inattentiveness and lack of interest failing concentration laziness and a certain negative attitude towards the school and its work in general *emotional disturbances* (behaviour disorders adaptation difficulties) further *physical defects* (defective senses somatic debility) *undesirable environmental conditions irregular school attendance* and possibly *inadequate teaching methods difficulties with regard to language and dialect immaturity*

The *primary reading retardation* (specific dyslexia) is according to *Hallgren* and others a hereditary disorder with dominant inheritance The incidence is about 10 per cent in the average population In its classical form it occurs

Table I
Reading quotient

III	0.20 – 0.29 = 13 0.30 – 0.39 = 23	36
II	0.40 – 0.49 = 47	47
I	0.50 – 0.59 = 17 0.60 – 0.69 = 11 ≥ 0.70 = 6	34

Explanation of table I Reading quotient $= \dfrac{\text{reading age}}{\text{school age}}$

series was divided into three groups on the basis of a graduation of the defect (the table begins with the poorest readers)

Reading age indicates the pupil s standard of reading A reading age of 2 years means that the pupil has attained the reading standard normally reached after 2 years of school attendance *School age* means the time the pupil has been taught at school Thus for instance a child with a reading age of 2 years who has attended school for 4 years has a reading quotient of 0 5

Practically all the children presented a grave combined *dyslexia – dys graphia* likewise indicated by a quantitative expression of the result of testing In assessing the reading disability too little attention is generally given to information on the dysgraphia accompanying the dyslexia Finally it is worth noting that all children referred to such specific remedial reading classes have prior to this been given special reading lessons in normal schools for one year Essential diagnostic importance should be attached to this fact with a view to eliminating possible exogenous factors which might simulate accentuate or conceal a specific predisposition to word blindness (see above)

The control series was carefully chosen among children in normal classes within the same municipality so as to correspond as closely as possible to the series of dyslectic pupils with regard to age sex classes (table 2) and range of intelligence quotients

Regarding ophthalmological examinations it is worth noting that, in addition to complete routine examination of all the pupils in cycloplegia the pupils concerned were also subjected to determinations of convergence and accom modation near points heterophoria test and evaluation of the binocular func tion [illegible] fusion reserves (synoptophore) and stereopsis

The following results were achieved

suggests at pointing out the ophthalmologist s role and at assessing the relevance of visual defects Collaboration between the medical and educational professions is necessary (*Goldberg Shearer*)

In the course of years an abundance of papers have been published dealing with investigations into the visual function in relation to reading difficulties in children The results achieved are sometimes contradictory and opinions are seen to have differed considerably with regard to the significance of visual defects as aetiological factors Some investigators adhere definitely to the view of a causal relationship, while others attach no importance to visual anomalies as the causes of specific dyslexia We quite agree with the latter This pronounced discrepancy is presumably due among other things to different views regarding the definition and genesis of dyslexia Series characterized as "poor readers "reading disability groups or "reading failures groups" (*Eames*) doubtless include other conditions besides those which we characterize in a purely medical sense as congenital word blindness or specific dyslexia The procedure of investigation and the importance attached to minor deviations from physiological standards are also likely to play a certain role (*H M Robinson*) a factor not unknown in this country

Be it emphasized that when asthenopia from different causes in the widest sense of the word is treated by a great variety of corrections this can by no means be identified with therapy or so called cure, of congenital word blindness If cure is obtained, this must be due to a mistaken diagnosis Visual anomalies may of course render reading extremely difficult but is not the cause of *specific dyslexia*

Our material was collected from a specific remedial reading class at a school in a well to do suburb of Copenhagen (*Hyldegårdsskolen*) We are greatly indebted to S A Tordrup Ph D former principal of the school and E Juel Christiansen head school psychologist for their thorough and exact educational and psychological testings of the dyslectic group and for having provided us with the required educational data We are also grateful for the careful selection of a useful control group to which we attach great importance

We believe that these word blind children have been so carefully selected as to constitute a representative group of the pupils affected with the disorder which within medical science must be characterized as specific dyslexia (or congenital word blindness)

The series of pupils concerned were as stated subjected to thorough and systematic psychological and educational testing and retesting All the pupils had a normal or high intelligence quotient 60 per cent above 110 The sex incidence showed preponderance of males The ratio of 4 1 accords with that commonly supposed A hereditary predisposition in one or more relatives was recordede in about 73 per cent The majority were found to have grave tardive reading defects defined quantitatively by a reading quotient (table I) The

Glasses had been prescribed to twice as many of the word blind as of the normal pupils

Visual Acuity and Refraction

None of the dyslectics were partially sighted The lowest binocular visual acuities were scarcely 6/9 (one case) and scarcely 6/6 (one case) The others had 6/6 or better

In the control series there were likewise found two with a scant 6/9 while the others had normal vision.

Only few pupils had monocular visual impairment equal numbers in the two series The most pronounced monocular visual impairment was found in the control series (table IV)

The retarded reading ability of the dyslectics was accordingly not due to impaired visual acuity

The great majority of both dyslectics and normals are emmetropic or slightly hypermetropic In the present series of word blind a minor preponderance of mild hypermetropia and slight astigmatism were noticed

Regarding refractive power the word blind did not differ significantly from the controls (table V)

Anisometropia of maximally 2 dioptres was noticed in eight of the word blind The same number occurred in the control series Anisometropia is thus a rare phenomenon having no influence on word blindness

Nine out of 117 dyslectics had glasses prescribed for the first time in relation to the present investigation

In two moderate myopia was now diagnosed for the first time In six cases mild hypermetropia (from + 1 25 sph to + 2 0 sph) was disclosed after dilatation of the pupil and sciascopy It is doubtful whether reading glasses

Table II
Visual acuity of poorest eye

	Dyslectics	Controls
≥ 6/6	105	105
< 6/6 – 6/9	7	5
< 6/9 – 6/12	[illegible]	2
< 6/12 – 6/18	[illegible]	1
< 6/18	1	6

Table II

	Dyslectics	Controls
boys	84 } 117	82 } 117
girls	33	35
age		
9 years	13	12
10 –	22	24
11 –	30	32
12 –	25	22
13 –	14	13
> 13 –	13	14
class at school		
3rd	12	13
4th	28	28
5th	29	24
6th	15	14
7th	13	22
8th	20	16

Past Histories

Subjective troubles were most frequent in the group of word blind Reading complaints were frequent as is not surprising such being a direct consequence of the pupil's dyslexia

Many of the word blind also complained of uncharacteristic conjunctival troubles (table III)

Table III
Subjective troubles

	Dyslectics	Controls
subjective troubles during near work	22	12
other subj troubles	29	16
previous prescription of glasses	31	16

Manifest strabismus was seen more frequently in the control series (9 per cent) than among the word blind (4 per cent)

The frequency of *latent strabismus* depends on the criteria chosen If we set the limit of exophoria at more than 8 prism dioptres there was found one case among the dyslectics and one among the controls Esophoria exceeding 4 dioptres was noticed neither among the dyslectics nor among the controls Hyperphoria exceeding 2 dioptres was observed in one word blind but in none of the controls

Narrower limits of exophoria (exceeding 6 prism dioptres) and hyperphoria (exceeding 1 prism dioptre) gave *preponderance of latent strabismus* in the word blind series (15 cases against 8 controls see table VI)

Such heterophoria is however compensated for by a considerable fusion reserve (table VIII) In no more than four cases were the fusion reserves so small that orthoptic treatment was indicated namely in three cases of exophoria (nos 2 57 and 84) and in one of hyperphoria (no 104)

In the control series one case was found in which orthoptic treatment might be advisable (no 109 exophoria)

There were no instances of divergence excess nor of convergence excess or insufficiency with a difference of more than 10 prism dioptres on the angle for distant vision compared with that for near vision

None of the other tests (heterophoria for distant vision stereopsis Bishop Harman s diaphragm test Worth s 4 light test fusion amplitude for distant and near vision covering test convergence near point and accomodation near point table VII) showed any significant difference between the word blind and the control group

Table VI

Bin cular functi n I 117 dyslectics and 117 controls Latent strabismus estimated by Maddox wing (30 cm)

		Dyslectics	Controls
ex ph ria	(> 6 prism di ptres)	7	[illegible]
es phoria	(> 4 ~)	0	0
hyperphoria	(> 1 ~)	9	1
latent strabismus Total		15	3
manifest strab smus		4	11
strab smus Total		19	14
rth pt c treatment indicated		4	1

Table 1
Refraction (Maximally refracting meridian stated)

		Dyslectics	Controls
hypermetropia emm	≦ + 1 0	53	70
	> + 1 0	29	23
	> + 2 0	5	3
	> + 3 0	2	2
	> + 4 0	2	3
myopia	≦ − 1 0	2	4
	> − 1 0	2	3
	> − 2 0	3	0
	> − 4 0	1	0
astigmat hypermetrop	≦ 0 5	11	3
	> 0 5	3	2
astigmat myop	≦ 0 5	4	2
mixed astigmat		0	2
Total		117	117

were necessary in these cases where the prescription may be characterized as an experiment

Fairly pronounced hypermetropia (+ 5 5 sph R E and + 4 5 sph L E) was found in one case only in which glasses were prescribed

In three cases previously prescribed glasses were withdrawn owing to the finding of emmetropia The previous correction was for slight hypermetropia (+ 0 5 ⊃ + 0 5 cyl 0 ° o u + 0 5 sph o u)

In seven cases previously prescribed glasses were altered Three myopic children had stronger glasses prescribed while two hypermetropes had theirs increased in strength by + 1 0 sph and one by 0 5 sph In one the strength was reduced by 0 5 sph

Of the controls, two had glasses prescribed for the first time while three had theirs altered None had their glasses withdrawn

Summarizing we may say that among the word blind children only one case of missed correction for hypermetropia was found a correction which probably would have improved the child s reading ability In the remaining cases the alterations performed were of doubtful value for the reading ability

Table VIII B

Fusion amplitude of dyslectics with hyperphoria exceeding 1 prism dioptre at 30 cm distance (Maddox wing)

pt no	Hyperphoria	Fusion amplitude		Convergence near point
	30 cm	30 cm	6 m	
10	3	+ 23 - 8	+ 17 - 6	3
24	2	+ 45 - 8	+ 45 - 6	4
45	2	+ 38 - 6	+ 25 - 4	3
62	2	+ 42 - 5	+ 20 - 4	3
70	2	+ 35 - 5	+ 18 - 6	5
72	2	+ 25 - 7	+ 16 - 6	7
76	3	+ 40 - 5	+ 15 - 6	4
104	2	+ 16 - 9	+ 12 - 6	11

Table VIII C

Fusion amplitude in control series of patients with exophoria exceeding 6 prism dioptres or hyperphoria exceeding 1 prism dioptre at 30 cm distance (Maddox wing)

pt no	deviation (phoria)	fusion amplitude		convergence near point
		30 cm	6 *m*	
103	10 exo	+ 45 - 7	+ 25 - 8	7
100	9 exo	+ 20 - 6	+ 20 - 4	11
91	2 hyper	+ 90 - 7	+ 25 - 6	3

treatment might be indicated These were three cases of exophoria and one of hyperphoria with small fusion reserves

Other Ophthalmological Findings

Colour sense Ishihara's test with colour plates gave abnormal colour vision in 9 per cent of the word blind and in 6 per cent of the controls

Surprisingly many (29 word blind and 35 controls) had initial difficulties of following quite accurately the winding lines of the colour plate.

Table VII

Binocular function of 117 dyslectics and 117 controls tested by means of Maddox cross synoptophore Bishop Harman etc.

	Word blind	Controls
ordinary covering test abnormal	11	14
heterophoria 4 m abnormal		
(same limits as in table VI > 6 > 4 > 1)	5	7
fusion amplitude 6 m (< 14 conv < 4 div)	20	19
fusion amplitude synoptophore		
(< 30 conv < 4 div)	33	3[illegible]
abnormal Bishop Harman or rod reading or W4L	13	15
convergence near point > 8 cm	6	10
accomodation near point > 10 cm	1	2
no stereopsis	5	8

Table VIII A

Fusion amplitude of dyslectics with exophoria exceeding 6 prism dioptres at 30 cm distance (Maddox wing)

pt no	Exophoria		Fusion amplitude		Convergence near point
	30 cm	6 m	30 cm	6 m	
2	8	3	+ 28 – 7	+ 6 – 6	4
18	8	0	+ 70 – 6	+ 20 – 6	4
49	8	0	+ 27 – 9	+ 16 – 4	[illegible]
57	8	2	+ 12 – 0	+ 8 – 6	9
84	11	8	+ 30 – 15	+ 20 – 12	4
97	8	2	+ 38 – 10	+ 16 – 8	5
98	8	2	+ 38 – 8	+ 20 – 6	6

Latent strabismus was thus perhaps slightly more frequent among the word blind children

However a deficient binocular function can only in very few cases if any have an influence on word blindness In the present series of 117 word blind children close orthoptic examination revealed four cases in which orthoptic

Table VIII B

Fusion amplitude of dyslectics with hyperphoria exceeding 1 prism dioptre at 30 cm distance (Maddox wing)

pt no	Hyperphoria	Fusion amplitude		Convergence near point
	30 cm	30 cm	6 m	
16	3	+ 25 – 8	+ 12 – 6	3
?4	2	+ 45 – 8	+ 45 – 6	4
45	?	+ 38 – 6	+ 2? – 4	3
6?	?	+ 42 – 5	+ 20 – 4	3
70	2	+ 35 – 5	+ 18 – 6	5
?	2	+ 25 – 7	+ 16 – 6	7
?6	?	+ 40 – 5	+ 18 – 6	4
104	?	+ 16 – 9	+ 12 – 6	11

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Fusion amplitude in control series of patients with exophoria exceeding 6 prism dioptres or hyperphoria exceeding 1 prism dioptre at 30 cm distance (Maddox wing)

pt no	deviation (phoria)	fusion amplitude		convergence near point
		30 cm	6 m	
101	10 exo	+ 4? – 7	+ ?5 – 8	7
109	9 exo	+ ?0 – 6	+ 20 – 4	11
91	? hyper	+ 90 – 7	+ 2? – 6	3

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57	8	2	+ 12 – 0	+ 8 – 6	9
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9[illegible]	8	2	+ 38 – 10	+ 16 – 8	5
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Latent strabismus was thus perhaps slightly more frequent among the word blind children

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advantage of the previously attempted therapy consisting in occlusion of the dominant eye to enforce accordance between hand and eye dominance (cf Shearer Eames)

Discussion and Conclusion

In the group of word blind children very few other pathological findings were made than this phenomenon and rarely abnormalities that were not equally often noticed in the control series

Slight hypermetropia and astigmatism may possibly occur a little more frequently among the dyslectics

In many cases the question of correction or not for a very mild hypermetropia and astigmatism must be a matter of opinion

The material shows that treatment of dyslectics with *glasses* had been attempted to a great extent even in cases with a doubtful indication for such treatment

Bifocal glasses with reading supplement may be indicated for partially sighted and in cases of convergence excess No such cases were found in the present series of word blind

Heterophoria indicating therapy was noticed in four cases only in which orthoptic treatment was preferred to correction by *prism glasses*

An incidence of 4 per cent of therapy requiring heterophoria hardly exceeds that to be expected in the normal population (cf convergence insufficiency indicating orthoptic treatment diagnosed in 2 per cent of patients seen in a Copenhagen practice (*Norn*))

We may conclude that the series of word blind under review had not been neglected therapeutically They seem to have been over treated if anything by glasses This is an understandable attempt at therapy in the individual cases

The results of this study thus afford evidence to suggest that visual defects bear no causal relation to *specific dyslexia* However this primary handicap may of course be intensified when visual anomalies playing a relevant part in near work including reading are present at the same time It rests with the ophthalmologist to take care that such are not overlooked

Summary

The present investigation comprised 11? word blind children constituting the total number of pupils from a school with specific remedial readings classes and a comparable control series of 11 pupils from a normal school

Conjunctivitis or blepharoconjunctivitis was noticed in 15 dyslectics and 11 controls

Corneal opacity incipient congenital cataract, vitreous opacities persistent pupillary membrane heterochromia iridis mild central ophthalmoscopic changes of no clinical significance etc were noticed in a few cases None of these abnormalities were particularly frequent among the dyslectics

In other words examinations by means of slit lamp, ophthalmoscope and colour plate disclosed no significant difference between dyslectics and controls

Non Ophthalmological Findings

Speech anomaly was found in 18 of the 117 dyslectics against only two of the controls

The speech anomalies of the dyslectics comprised mainly lisping and stuttering

The *intelligence quotients* were high averaging 111 % No more than eight were under 100 % and none under 90 % This is in keeping with the fact that the school for dyslectics does not receive mentally defective children

Hearing defects occurred in two word blind children

Right-left dominance Most people prefer to use the right eye for monocular work (e g fore sight monocular telescope and microscope) This was also the case with the majority of the dyslectics left eye dominance or ambivalence having been noticed in no more than 37 word blind against 43 controls

Left handedness was rare and definite combinations of dominant eye and dominant hand could not be said for certain to exist The combination of right hand and left eye seemed however to be slightly rarer among the dyslectics than in the control group (table IX)

This finding argues definitely against a crossed hand and eye dominance in association with word blindness and consequently also against any

Table IX

Dominant eye and dominant hand of 117 word blind children and 117 controls

	Dyslectics	Controls
lt eye and lt hand	9	6
lt eye and rt hand	28	37
rt eye and lt hand	5	4
rt eye and rt hand	75	70

advantage of the previously attempted therapy consisting in occlusion of the dominant eye to enforce accordance between hand and eye dominance (cf *Shearer Eames*)

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Summary

The present investigation comprised 11 word blind children, constituting the total number of pupils from a school with specific remedial readings classes and a comparable control series of 11 pupils from a normal school

The examinations performed showed that word blindness (dyslexia) is not due to refractive errors impaired visual acuity or orthoptic disorders

A *doubtful preponderance was noticed of mild hypermetropia slight* astigmatism and latent strabismus to near vision Orthoptic treatment was indicated in 4 per cent of these cases

There was no preponderance of crossed eye hand dominance

The conclusion was drawn that word blind children should be subjected to particular careful ophthalmological examination to prevent possibly existing visual anomalies from accentuating the true reading difficulties

No causal relation exists between specific dyslexia and visual defects in their widest sense

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PSEUDOEXFOLIATION OF THE LENS CAPSULE
II DEVELOPMENT OF THE EXFOLIATION SYNDROME

BY

EGILL HANSEN and OLE JACOB SELLEVOLD

The high frequency of glaucoma amongst patients with pseudoexfoliation of the lens capsule has caused many ophthalmologists to regard pseudoexfoliation as a sign of pre glaucoma and to consider patients in whom changes of this kind are observed as being particularly liable to develop glaucoma *Gifford* (195) believes that the complete exfoliation syndrome is developed over a considerable length of time a matter of ten to twenty years rather than three to five years *Tarved* (1964) and *Klouman* (1967) believe that in the majority of cases where glaucoma occurs in eyes with pseudoexfoliation it develops simultaneously with or shortly after the appearance of pseudoexfoliation and that the risk of glaucoma developing later is small

However the tendency may be in the development of the exfoliation syndrome there would appear to be many exceptions Most ophthalmologists know examples of patients in whom pseudoexfoliation has been observed and watched over a number of years without glaucoma having developed whilst other patients may have contracted glaucoma after short as well as long periods of observation Very few follow up examinations have been conducted on persons with pseudoexfoliation of the lens capsule The purpose of the present paper is to try to throw more light on the process of development of the exfoliation syndrome The basis for this work has been provided by our exfoliation material from Namdal Hospital (Acta Ophthal 46 1095 1104) these patients having been subjected to continual observation and check ups with the

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This investigation was partly supported by a grant from Dr Nils Helsingens Foundation for Medical Research at Namdal Hospital

[illegible]

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EGILL HANSEN and OLE JACOB SELLEVOLD

The high frequency of glaucoma amongst patients with pseudoexfoliation of the lens capsule has caused many ophthalmologists to regard pseudoexfoliation as a sign of pre glaucoma and to consider patients in whom changes of this kind are observed as being particularly liable to develop glaucoma *Gifford* (195) believes that the complete exfoliation syndrome is developed over a considerable length of time a matter of ten to twenty years rather than three to five years *Tarred* (1964) and *Klouman* (1967) believe that in the majority of cases where glaucoma occurs in eyes with pseudoexfoliation it develops simultaneously with or shortly after the appearance of pseudoexfoliation and that the risk of glaucoma developing later is small

However the tendency may be in the development of the exfoliation syndrome there would appear to be many exceptions Most ophthalmologists know of examples of patients in whom pseudoexfoliation has been observed and watched over a number of years without glaucoma having developed whilst other patients may have contracted glaucoma after short as well as long periods of observation Very few follow up examinations have been conducted on persons with pseudoexfoliation of the lens capsule The purpose of the present paper is to try to throw more light on the process of development of the exfoliation syndrome The basis for this work has been provided by our exfoliation material from Namdal Hospital (Acta Ophthal 46 1095 1104) these patients having been subjected to continual observation and check ups with the

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object of obtaining the most complete follow up records possible Being the only ophthalmological service department in our hospital district we have benefited from the fact that long-term control of patients has had to be conducted at the hospital Moreover, during recent years patients have been called in systematically with the object of ensuring regular annual check ups

Bilateral development of pseudoexfoliation in patients in whom unilateral pseudoexfoliation has originally been observed

Amongst patients with unilateral pseudoexfoliation a number have developed pseudoexfoliation in the other eye in the course of the period of observation in all 45 men and 73 women Fig 1 shows distribution by age for these patients when the presence of pseudoexfoliation was observed for the first time likewise distribution by age for the same patients when pseudoexfoliation was observed in the other eye As there is no great deviation from normal distribution the curves have been shown here on probability graph paper It will be observed that the curves run approximately parallel which indicates that the period of time which elapses before pseudoexfoliation is detected in the other eye is not to any appreciable degree dependent on the age of the patient The overall picture is the same for men as for women The average age at which pseudoexfoliation was observed in the first eye was 68 7 years for men

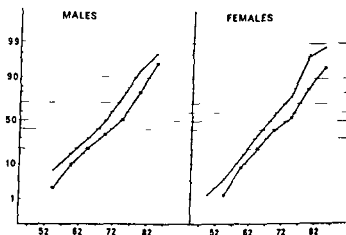


Fig 1

Cumulative frequency polygons showing distribution by age in respect of 45 men and 73 women at the time when unilateral pseudoexfoliation was first noted (top curve) likewise distribution by age in respect of the same patients when bilateral pseudo exfoliation was detected (bottom curve)

Age is indicated along the abscissa and realtive frequency along the ordinate

(S D = 8.98 years) and 67.8 years for women (S D = 8.82 years) and the average age at which bilateral pseudoexfoliation was observed was 72.4 years (S D = 8.53 years) and 71.9 years (S D = 8.34 years) for men and women respectively

Figs 2 and 3 show the development of bilateral pseudoexfoliation in relation to the number of patients observed Amongst patients who had originally contracted unilateral pseudoexfoliation 40.8 % of the men and 31.0 % of the women developed bilateral pseudoexfoliation within the course of a 5 year period of observation The incidence of bilateral pseudoexfoliation revealed a tendency to increase when the period of observation was protracted

Development of glaucoma in patients with unilateral pseudoexfoliation

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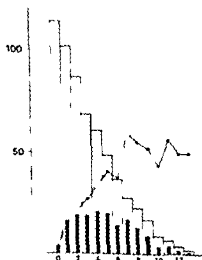


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Incidence of pseudoexfoliation in the other eye in men in whom pseudoexfoliation was registered from the outset as being unilateral The number of patients is indicated along the ordinate The figures along the abscissa indicate the number of complete years during which the patients were kept under observation. The white columns show the total number of patients under observation and the black columns how many of them have contracted bilateral pseudoexfoliation. The curve shows the incidence of pseudoexfoliation in the other eye expressed as a percentage the figures along the ordinate also indicate the percentage

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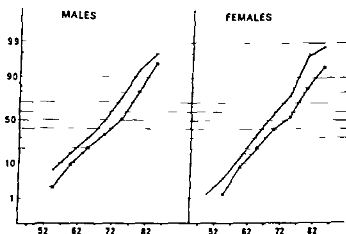


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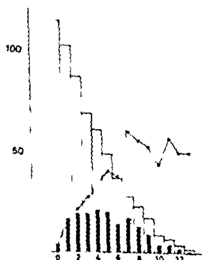


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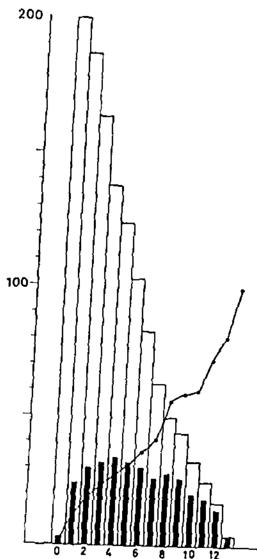


Fig 8
Incidence of pseudoexfoliation in the other eye in women in whom pseudoexfoliation was registered from the outset as being unilateral Key to signatures as for fig 9

148 women who did not have glaucoma to start with The results of these observations are shown in figs 4 and 5 The criteria for glaucoma have been gone into in an earlier paper (Acta Ophthal 46 1095 1104)

In a number of cases in which it was feared that glaucoma might develop pseudoexfoliation patients were given glaucoma medication even though glaucoma had not actually been observed as a rule pilocarpine drops once or twice a day were administered It is doubtful whether such medication was able to mask the development of glaucoma In the diagrams however we have marked patients who received such medication with unbroken horizontal lines

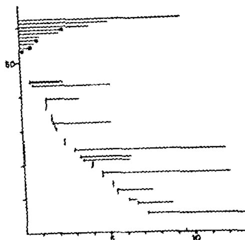


Fig 4

Results of observation carried out on 63 men who originally had unilateral pseudo exfoliation but in whom glaucoma was not present at the outset. Each individual patient is marked on the diagram The black dots indicate the occurence of glaucoma The vert cal lines show the length of time the patients were kept under observation without glaucoma having been observed The horizontal lines indicate that the patients were kept under observation while receiving glaucoma medication The figures along the abscissa indicate the period of observation in years and the ordinate shows the number of patients

corresponding to the length of the period of observation patients who received medication from the beginning are placed at the top Each individual patient has been plotted into the graph Patients kept under observation for the longest periods *without glaucoma developing* are placed at the bottom In cases where intraocular operations were performed (for cataracts damage etc) the periods of observation have been classified as discontinued as from the dates of such operations

Periods of observation varied a great deal Out of the 63 men observed (fig 4) glaucoma developed during the first 2 years in 5 patients (8 %) in the course of 5 years in 9 patients (14 %) and in the course of 10 years in 12 patients (19 %) After periods of 2 5 and 10 years respectively glaucoma had still not developed in 62 % 38 % and 5 % of the original 63 patients Many of the patients however drop out as a result of curtailment of the period of obser vation

Out of the 148 women observed (fig 5) glaucoma developed in 9 patients (6 %) during the first 2 years in 17 patients (12 %) during the first 5 years

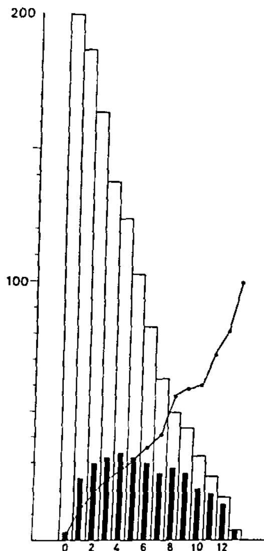


Fig 3

Incidence of pseudoexfoliation in the other eye in women in whom pseudoexfoliation was registered from the outset as being unilateral Key to signatures as for fig 2

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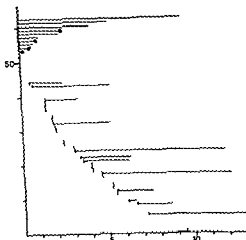


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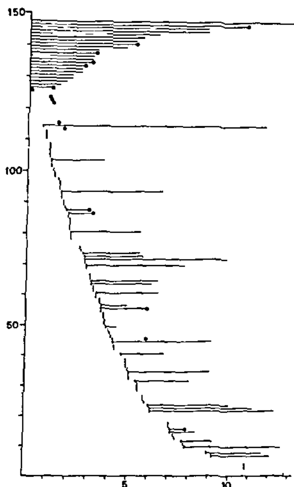


Fig 5
Results of observation carried out on 148 women who originally had unilateral pseudoexfoliation but in whom glaucoma was not present at the outset Key to signatures as for fig 4

and in 26 patients (18 %) in the course of 10 years After periods of 2 5 and 10 years respectively 74 % 37 % and 10 % of the original 148 patients had still not contracted glaucoma

Development of glaucoma in patients with bilateral pseudoexfoliation

Amongst patients with pseudoexfoliation in both eyes we have had the opportunity of following the course of development in 46 men (92 eyes) and in 81 women (155 eyes) who originally did not have glaucoma in either eye The results of these observations are shown in figs 6 and 7

After 2 years glaucoma had developed in 11 % of the 46 men under observa

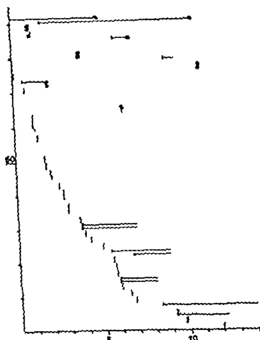


Fig 6

Results of observation carried out on 92 eyes in 46 men who originally had bilateral pseudoexfoliation but in whom glaucoma was not present at the outset. The eyes of each patient are marked in pairs. The black dots indicate the occurrence of glaucoma. The vertical lines show the length of time the patients were kept under observation without glaucoma having been observed. The horizontal lines indicate that the patients were kept under observation while being on glaucoma medication. The figures along the abscissa indicate the period of observation in years and the ordinate shows the number of eyes

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Amongst the 81 women observed 5 % (4 patients/ 7 eyes) had contracted glaucoma within the first 2 years, % (6 patients/ 10 eyes) in the course of 5 years and 9 % (patients/ 11 eyes) in the course of 10 years. After 2, 5 and 10 years of observation respectively 74 %, 38 % and 6 % of the original 81 patients had still not contracted glaucoma.

From figs 6 and 7 it can be seen that there is a tendency to paired grouping of the flakes marking the presence of glaucoma, i e both eyes tend to follow

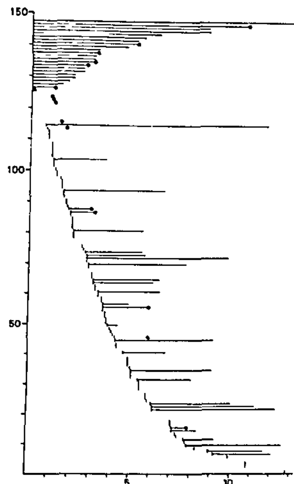


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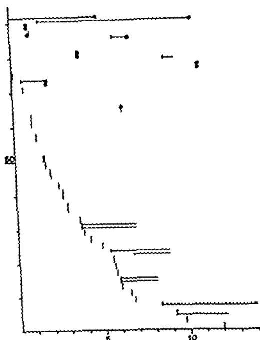


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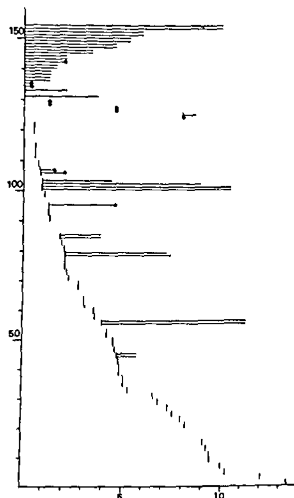


Fig 7
Results of observation carried out on 155 eyes in 81 women with bilateral pseudo exfoliation but in whom glaucoma was not present from the outset Key to signatures as for fig 6

one another in the development of glaucoma In all glaucoma occurred in 1? men in 20 eyes (fig 6) In the case of 4 of these men glaucoma was detected in both eyes at the same time and in the case of 3 patients in both eyes within a period of 6 months Amongst the women glaucoma was detected in 8 patients in 13 eyes (fig 7) in 4 of these patients glaucoma was detected at the same time in both eyes and in 1 patient it was observed in both eyes within a period of 6 months

So as to obtain a clearer picture of the tendency for glaucoma to develop in the other eye when already present in one eye we have placed all patients with bilateral pseudoexfoliation and glaucoma in one eye in one group Fig 8 shows further development in respect of the other eye in these patients 2?

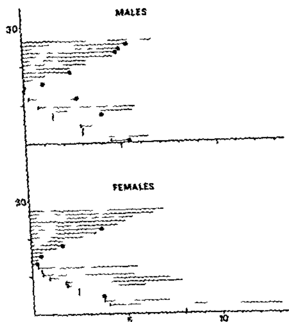


Fig 8

Results of observation carried out on the other eye in 27 men and 28 women with bilateral pseudoexfoliation in whom glaucoma was present in one eye from the outset. Key to signatures as for fig 4

men and 28 women After 2 years of observation 2 of the men (7 %) and 4 of the women (14 %) had developed glaucoma in the other eye After 5 years glaucoma had manifested itself in the other eye in 7 men (26 %) and 6 women (21 %) At the same time 18 of the original 27 men (67 %) were kept under observation for 2 years without contracting glaucoma and 6 men (22 %) for 5 years without getting glaucoma After periods of observation of 2 and 5 years respectively 20 (71 %) and 12 (43 %) of the original 28 women had still not contracted glaucoma

As will be apparent from the foregoing diagrams glaucoma manifested itself in patients with pseudoexfoliation after greatly varying intervals of time If we regard the cases in which glaucoma developed during the period of observation and where the course of such development was not influenced by any form of medication (fig 9) we find no marked tendency to any increase in the length of interval towards either lower or higher age groups This would seem to indicate that the interval elapsing between the first time

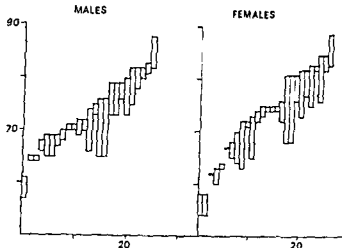


Fig. 9

Development of glaucoma in 20 men (25 eyes) and 24 women (27 eyes) seen in relation to the patients' ages. Each eye is indicated by a column whose base indicates the patient's age when pseudoexfoliation was first observed, the top of the column indicates the age at which glaucoma was detected.

pseudoexfoliation is detected until glaucoma develops is not influenced by the age of the patient. The average interval of time in respect of the 20 men is 3.7 years (S.D. = 2.84 years) and for the 24 women 4.4 years (S.D. = 2.93 years).

Comments

Amongst those of our patients who originally had unilateral pseudoexfoliation a considerable number developed pseudoexfoliation in the other eye in the course of the period of observation. The incidence of bilateral pseudoexfoliation increased with the prolongation of the period of observation. This would indicate that the development of pseudoexfoliation is a general process with a tendency to affect both eyes. In many patients, however, pseudoexfoliation remains unilateral over a number of years or for ever, as claimed by *Tarkkanen* (1962). Tarkkanen observed 17 patients with unilateral pseudoexfoliation over a period of 5 years and found, in contrast to our findings, that none of his patients had contracted pseudoexfoliation in the other eye.

An interesting trait is the difference in average age at which pseudoexfoliation is observed in the first eye compared with the average age at which bilateral pseudoexfoliation is detected. The average ages at which the unilateral

and bilateral phases commenced likewise the average difference in age tally fairly well with the corresponding figures worked out in respect of the material as a whole when dividing it into groups of cases of unilateral and bilateral pseudoexfoliation respectively (Acta Ophthal 46 1095 1104) All in all our findings would seem to indicate that unilateral pseudoexfoliation is an early and bilateral pseudoexfoliation a later stage of the exfoliation syndrome

It has been estimated that in approximately 10 % of a given number of observed cases pseudoexfoliation may not be noticed if the pupil is not dilated (*Aasved* 1965) The reservation must therefore be made that some patients with bilateral pseudoexfoliation may have been included in the unilateral pseudoexfoliation group as the majority of patients have not been subjected to mydriasis at their first examination In such instances however the degrees of pseudoexfoliation present in the two eyes will have been different In all circumstances we are dependent upon the fact that the process of pseudoexfoliation has to reach a certain stage before we are able to register it *Gifford* (1957) points out that we are not dealing with static identical conditions but with a process that changes continuously one in which conditions vary from one individual to the next It is therefore only reasonable to expect the same kind of variation in two eyes belonging to the same individual

Whilst glaucoma was already detected in 31 % of the women and 45 % of the men at the same time as pseudoexfoliation was observed (Acta Ophthal 46 1095 1104) subsequent examination of the remaining patients in the material revealed that glaucoma was contracted by 14 % to 20 % of the men and [illegible] % to 12 % of the women within a 5 year period of observation and by 19 % to 24 % of the men and 9 % to 18 % of the women in the course of a 10 year period The figures quoted here are minimum as a considerable number of the patients were not kept under observation for a sufficiently long time On the other hand at least 38 % to 44 % of the men and at least 37 % to 38 % of the women did not contract glaucoma after a 5 year period of observation The danger of glaucoma developing in patients with pseudoexfoliation within this period of time is therefore not acute

The investigation revealed that glaucoma can develop at any time after pseudoexfoliation has been observed In some cases glaucoma has only developed after the elapse of 10 years but several patients have been kept under observation for more than 10 years without contracting glaucoma In our material no particular tendency has been observed for glaucoma to develop during the initial period following upon the detection of pseudoexfoliation as has been presumed by *Aasved* (1964) and *Kloumann* (1967) However we have no information in respect of the largest group of glaucoma patients as to how glaucoma actually developed i e in respect of those who were already found to be suffering from glaucoma when pseudoexfoliation was first observed It is therefore possible that in the majority of patients developing glaucoma the

development may be very early if not coincident with the appearance of pseudoexfoliation Nor can we eliminate the possibility that the very initial stage of development of glaucoma in these patients may have commenced *before* the formation of pseudoexfoliation in other words that a pre glaucomatous condition may even be the basis for the exfoliation process However it is seldom that pseudoexfoliation develops in eyes in which glaucoma has previously been observed (*Bertelsen et al* 1965, *Roche* 1968)

When glaucoma develops in patients with bilateral pseudoexfoliation there is a marked tendency for it to occur in both eyes simultaneously or within a limited period of time In cases where glaucoma is already present in the one eye and bilateral pseudoexfoliation has also been observed the chances of glaucoma developing in the other eye as well are very great in our material glaucoma developed in the other eye in at least 21 % to 26 % of our patients within the first 5 years (fig 8) These figures are presumably very low compared with the true figures as a considerable number of the patients had not been kept under observation for a sufficiently long period of time or else had been observed while receiving full glaucoma medication Our results agree with those obtained by *Tarkkanen* (1962) who found that once glaucoma had developed in patients with bilateral pseudoexfoliation there were always glaucomatous signs in *both* eyes as outflow impairment could be proven bilaterally in all his cases More systematic investigations of patients at the pre glaucomatous stage would presumably throw more light on the relationship between pseudoexfoliation and glaucoma

Summary

Development of the exfoliation syndrome has been registered in patients in whom unilateral and bilateral pseudoexfoliation were originally observed A comparatively large number of the patients with unilateral pseudoexfoliation contracted bilateral pseudoexfoliation in the course of the period of observation. The incidence of cases of bilateral pseudoexfoliation increased with the protraction of the period of observation After 5 years bilateral pseudoexfoliation had developed in 40 8 % of the men and 31 0 % of the women who originally only had unilateral pseudoexfoliation

Amongst pseudoexfoliation patients who did not have glaucoma to start with glaucomatous development was found in 7 % to 20 % after 5 years observation and in 9 % to 24 % after 10 years These are minimum figures In cases of bilateral pseudoexfoliation there was a pronounced tendency for glaucoma to develop simultaneously in both eyes Patients with bilateral pseudoexfolia

tion and glaucoma in one eye are particularly exposed to the risk of contracting glaucoma in the other eye Glaucoma which occurs in eyes in which pseudoexfoliation has been observed is likely to develop at any time after the detection of pseudoexfoliation The investigation confirms the need of regular continuous check ups for all patients in whom pseudoexfoliation has been observed

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RELAPSING POLYCHONDRITIS

Report of a case presenting multiple ocular complications

BY

BJÖRN BERGAUST and ARNE M ABRAHAMSEN

The syndrome relapsing polychondritis is characterized by recurrent attacks of painful inflammation of hyaline cartilage A comprehensive account of the syndrome was published by *Dolan et al* in 1966 These authors described 2 cases and found 49 more cases on going through the literature Since then some more cases have been published *Diebold et al* (1966) *Riggs* and *Wilson* (1967) and *Anderson* (1967) The first Scandinavian descriptions were published by *Jensen* (1962) in Denmark and by *Goldwater* (1963) in Norway

In this article a typical case will be described An especially interesting aspect of this case was *the multiple eye complications* perhaps more varied than previously described in a patient The general symptoms have been described in more detail elsewhere *(Abrahamsen* and *Bergaust* 1969)

Case No 26 261/66 The patient was a 27 year old previously healthy man The disease started in September 1964 as a febrile illness with inflammation of the left auricular cartilage After 3 weeks inflammation of the nasal cartilage developed with destruction and permanent deformation of the nose The left auricular cartilage was also permanently deformed and stood out more than normal (Fig 1) Later the patient developed symptoms of inflammation of the costal cartilages The latter symptoms recurred after a few months with simultaneous back pain and pain in the left knee The patient was treated at Ullevål Hospital Dept VII The ESR was greatly increased up to 127 mm hour The haemoglobin was rather low down to 10 2 g 100 ml A biopsy from the nasal septum showed chronic perichondritis and chondritis (Fig 2) LE cell test anti streptolysin titre immune serum electrophoresis

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Fig 1 a) b) c)
Deformity of nose and left ear

and serum amino acid chromatography were all normal Sugar chromatogram from the urine was slightly irregular but no definite conclusions could be drawn from it. The patient was treated with Monophenylbutazone with a good effect on the inflam mato y sympt ms

Eye compli ations appeared just less than a year after the onset of symptoms In July 1965 he developed severe episcleritis and iridocyclitis in the left eye There was



Fig 2
Biopsi specimen from septum nasi Perichondritis and chondritis

also pain in the right hip joint and over the costal cartilages The ESR was 90 mm/hour Six months later he developed a curious acute sclerokeratitis in the same eye (Fig 3) There was corneal oedema and numerous infiltrates in the corneal stroma These infiltrates were almost discoid in shape with a diameter of up to 1 mm Only over two more superficial infiltrates was the epithelium affected After six months freedom from symptoms there was a recurrence of the same type of sclerokeratitis in the left eye In October 1966 acute pain developed in both eyes There was then aqueous flare in the anterior chamber of both eyes with many corpuscles and an increased number of corpuscles in the vitreous body In the right fundus oculi there were two large cloudy yellowish chorioretinal infiltrates and in the left fundus a similar large central infiltrate The appearance was rather reminiscent of Coats retinitis (Fig 4) Visual acuity was then right eye 6/6 left eye fingers at 2 m ESR was 12 mm/hour General treatment with Prednisolon and local treatment with Atropine and Cortisone was given The fundus changes rapidly became quiescent and after 2 weeks the infiltrates were inactive with pigmentations (Fig 5) Visual acuity in the left eye improved to 6/40 which it has remained since While the patient was still being given general treatment with Prednisolon there was a new flare up of the sclerokeratitis in February 1967 The patient was then symptom free for a year after which there was a new attack of the same type of sclerokeratitis ESR 3 mm/hour The recurrent sclerokeratitis has improved slightly when treated with Atropine and Chloramphenicol drops but it has always rapidly become quiescent with Cortisone drops The last two recurrences only lasted 3–4 days with this treatment



Fig 3
Sclerokeratitis Limbal injection and corneal infiltrates



Fig 4
Part of retinal infiltrate Cotton wool like active stage



Fig 5
Part of another retinal infiltrate Inactive stage

Summary

The patient had painful recurrent attacks of inflammation of hyaline cartilage affecting the auricular cartilage nasal cartilage costal cartilages and knee Biopsy showed perichondritis and chondritis ESR was markedly raised Hb rather low Sometimes at the same time as the cartilage inflammation and raised ESR sometimes independently the patient has had sclero iritis once a special type of sclerokeratitis 4 times and bilateral panuveitis with exudative chorioretinitis once The eye inflammation has responded well to Cortisone preparations

Discussion

Relapsing polychondritis was first described by Jaksch Wartenhorst in 1923 who called the syndrome polychondropathia The disease has no simple pathognomonic sign There are generally recurrent attacks of painful inflammation affecting hyaline cartilage It has most often been described affecting the auricular and nasal cartilage There is often also inflammation in peripheral

joints larynx trachea and costal cartilages Our patient had inflammation in the nose ear ribs and knee There should be involvement of hyaline cartilage in 2-3 places before the diagnosis can be made (*Kaye* and *Sones* 1964) Inflammation in the tracheo bronchial tree can be very serious Several patients have died as a result of occlusion of the respiratory tract Other patients have been saved by tracheostomy There is fever in the acute stage of relapsing polychondritis and our case began like this A raised ESR has frequently been described Our patient had a high ESR in connection with the chondritis but only the first time there was inflammation of the eye Anaemia as shown in our patient is found in over half the cases A low serum albumin and a raised serum globulin were demonstrated in our patient and are also often found The inner ear may be affected with tinnitus and vertigo There may also be leg oedema adenopathy myocarditis and signs of abnormal liver function All the findings mentioned above are most pronounced in the acute phases of the disease The diagnosis must be made on the basis of the clinical findings which must be said to be convincing in the present case Cartilage biopsy can support the diagnosis In the acute phases there is inflammation affecting hyaline cartilage There is loss of normal basophilia achondrolysis and round cell infiltrates In the later stages there is fibrosis Our biopsy was taken after the acute changes were over and the findings agree with this The cartilage changes are probably due to loss of chondroitin from the cartilage matrix This polysaccharide may be the cause of the abnormal sugar chromatogram in the urine (Kaye and Sones)

The inflammatory changes usually start in hyaline cartilage Eye complications are very common appearing a varying interval after the onset of the disease In our patient the eye symptoms developed just under a year after the onset as episcleritis and iridocyclitis As many as 60% of the cases described have had conjunctivitis or episcleritis (*Dolan et al* 1966) According to these authors iritis has been found in 27% of cases which is a strikingly high incidence For comparison it can be remembered that 15 to 50% of patients with ankylosing spondylitis develop iritis at some stage (*Godtfredsen* 1949) Keratitis has also been described before as a complication The curious sclerokeratitis which was a prominent feature in our patient has not often been described It seems to agree well with a case of episcleritis and opacities in the corneal parenchyma near the episcleritis reported by *Degos et al* (1960) *Kaye* and *Sones* (1964) mentioned that one patient had chorioretinitis but this is not described in more detail We have only been able to find one description in the literature of relapsing polychondritis in which there were symptoms comparable to the pronounced exudative chorioretinitis seen in our patient (*Anderson* 1967) We have not been able to find a description of a patient with so many recurrences of different types of eye inflammation It was remarkable how rapidly the ocular complications healed leaving little sequelae



Fig 5
Part of another retinal infiltrate Inactive stage

Summary

The patient had painful recurrent attacks of inflammation of hyaline cartilage affecting the auricular cartilage nasal cartilage costal cartilages and knee Biopsy showed perichondritis and chondritis ESR was markedly raised Hb rather low Sometimes at the same time as the cartilage inflammation and raised ESR sometimes independently the patient has had sclero iritis once a special type of sclerokeratitis 4 times and bilateral panuveitis with exudative chorioretinitis once The eye inflammation has responded well to Cortisone preparations

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In our patient the course of the disease was benign He retained good vision and after having been unfit for work for the first 1½ years of the disease he has since been fully active as an industrial worker

Other eye complications have been described Sjögren s syndrome exophthalmus with muscle paralysis (*Rucker* and *Ferguson* 1965) detachment of the retina cocco central scotoma and progressive scleral thinning (*Anderson* 1967)

The nature of the disease is under investigation It is possible to simulate the cartilage changes by injecting rabbits with papain This results in flopping of the ears because of loss of chondroitin from the cartilage matrix Overdosage with vitamin A can lead to excessive production of proteolytic enzyme from the cartilage cells and result in destruction of cartilage matrix This is however not the cause of the cartilage changes in polychondritis There is much to indicate that it is connected with the immune reaction Direct fluorescein – antibody investigations have demonstrated greater fixation to the cartilage cells with conjugated patient serum than with normal serum (*Dolan et al* 1966) The connection between chondritis and eye inflammation is also unknown but may be related to the presence of large amounts of mucopolysaccharides in both cartilage and the eye

Summary

A case of polychondritis is described The patient had inflammation of hyaline cartilage in the ears nose costal cartilages and knee There were recurrent eye complications sclero iritis sclerokeratitis several times and bilateral panuveitis with exudative chorioretinitis once The eye symptoms responded well to Cortisone preparations The cause of the disease is not known

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In sequence eyes with a primarily defect drainage system are easier affected In fact a high percentage of additional primary glaucoma (65–82 per cent) has been found in series studied by tonography (*Maumenee* 1959 *Vannas* and *Tarkkanen* 1960 *Becker* and *Shaffer* 1961 *Raitta* 1965)

Aqueous humor dynamics after central retinal vein occlusion has formerly been paid little attention to In a recent study (*Raitta Vannas* and *Aurekoski* 1968) hemorrhagic glaucoma was shown to develop slowly It can be suspected by the development of an aqueous flare increasing outflow resistance and iris neovascularisation Therefore therapy should be set in early in order to prevent the blocking effect of the hematogenic disintegration products

Desferrioxamin is a chelating agent capable to bind iron from all human iron containing proteins (*Wohler* 1962) It has been used as a therapeutic agent in iron storage disease and iron poisoning (*Dyerberg* 1967) In ophthalmologic practice it was shown effective in ocular siderosis and hemochromatosis (*Falbe Hansen* 1966)

Desferrioxamin B in the treatment of hemorrhagic glaucoma was suggested by *Valvo* (1966) It seems to have no effect in fully developed hemorrhagic glaucoma (*Vannas* and *Raitta* in press) In consequence to the theoretic aspects on the possible pathomechanism of hemorrhagic glaucoma desferrioxamin B (Desferal®) was given prophylactically to a series of 10 patients with central retinal vein occlusion

Material and Methods

The material consisted of 10 patients (6 females and 4 males) with central retinal vein occlusion On hospitalisation anticoagulant treatment was started immediately Intramuscular injections of B desferrioxamine (Desferal®) 1 g/die for two weeks was given simultaneouly Repeated biomicroscopy applanation pressure recordings and tonographies were made Hemorrhagic glaucoma was defined as grossly elevated pressure (at least above 30 mm Hg) and rubeosis iridis with shortening of the chamber angle

Results

None of the cases developed hemorrhagic glaucoma during the time of observation which in all cases was 4 months or more (Table II)

From the Helsinki University Eye Clinic
(Head: Prof. Salme Vannas, M.D.)
Helsinki, Finland

DESFERRIOXAMINE B IN THE PREVENTION OF HEMORRHAGIC GLAUCOMA

BY

CHRISTINA RAITTA and SALME VANNAS

The pathogenesis of hemorrhagic glaucoma after central retinal vein occlusion is not yet understood. Several theories have been presented (Table I). Emphasis has been paid to two main causes: blockage of aqueous humor drainage and arterial involvement.

Blood disintegration products, hemosiderin and other ironpigments seem

Table I
Theories on the pathogenesis of hemorrhagic glaucoma

Author	Year	Theory
Coats	1913	Blockage of drainage system by albumin compounds
Leber	1914	Additional arterial changes
Wood	1932	Vitreous swelling
Samuels	1935	Albumin compounds and a vascular membrane in the chamber angle due to toxic blood distintegration products
Weinstein	1939	Vitreous swelling due to acid compounds
Vannas	1960	Iron compounds like hemosiderin and hemosiderin filled macrophages as blocking agents

Desferal® (Ciba) was supplied by Ciba Ltd. Helsinki.
For this we want to thank Mr. B. Jaatinen, Managing director.
Received July 6th 1968.

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Table II

Age and sex distribution treatment and time of observation in a series of 10 patients treated with desferrioxamine B

Sex	Age (years)	Time since occlusion	Observation time (months)	Additional primary glaucoma	Anticoagulant therapy
Female	76	1 month	4	–	–
Female	51	3 weeks	4½	–	–
Female	55	2 days	5½	–	–
Female	73	1 month	5½	–	–
Female	58	1½ month	5½	–	+
Female	55	2 weeks	4½	–	–
Male	77	1 week	6	–	–
Male	41	1½ month	21½	–	+
Male	58	1 day	4½	–	–
Male	42	1 week	6½	–	–

The course of case 8 is most illustrative During the follow up this patient with primarily heavy hemorrhages (Fig 1) developed an aqueous flare and irisneovascularisation (Fig 2) All signs that were indicative for hemorrhagic glaucoma Outflow resistance increased (Fig 3) and treatment with desferrioxamine B was instituted Hemorrhagic glaucoma did not develop 14 months later a vitreous hemorrhage occured and imminent signs of hemorrhagic glaucoma developed Therefore desferrioxamine b treatment was repeated The pressure level is now satisfactory residual hemorrhages in the vitreous and irisneovascularisation seen in angiography are still present

Discussion

The pathomechanism of hemorrhagic glaucoma is not yet fully understood The role of *ironcontaining blood disintegration products* (*Vannas* 1960 a) by *Vannas Tarkkanen* and *Raitta* 1966) seems clear Additional factors like arterial insufficiency may also be present In the series of *Tiburtius* (1960) and *Vannas* and *Raitta* (1966) anticoagulant treatment decreased the incidence of hemorrhagic glaucoma



Fig 1
Heavy hemorrhages after occlusion of the central retinal vein

Entirely new possibilities were created with the use of a chelating agent in ironstorage disease and iron intoxication *Wohler* (1962) Desferrioxamine B was suggested by *Valvo* (1966) in the treatment of hemorrhagic glaucoma Recent studies (*Raitta Vannas* and *Aurekoski* 1968) show that hemorrhagic glaucoma develops slowly and can be forseen by signs like an aqueous flare increasing outflow resistance and iris neovascularisation In consequence chelates should be used prophylactically and instituted immediately after the occlusion Treatment must be repeated if during the posthrombotic course imminent signs reappear

The number of patients does not allow definite conclusions We are however convinced that ironchelates offer a valuable aid in the treatment of hemorrhagic glaucoma

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Female	55	2 weeks	7½	−	−
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course of one imminent case gives strong evidence that prophylactic treatment with an iron chelate decreases the incidence of hemorrhagic glaucoma No complications that could be related to Desferal® were seen

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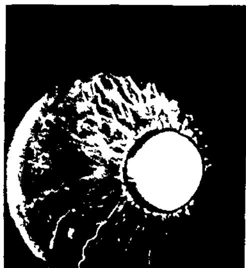




Fig 2

Fluorescein angiogram of iris vessels 20 months after central retinal vein occlusion
a) Neovascularisation seen as fluorescent dots at pupillary border and in the periphery
b) Late phase showing diffuse leakage
Normal intraocular pressure level

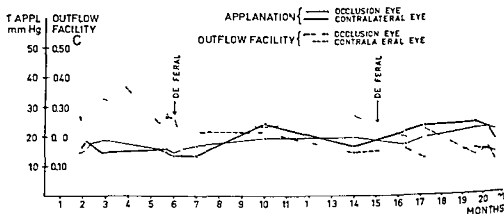


Fig 3

Pressure and C curves during 21½ months after occlusion of the central retinal vein

Summary

During one year a series of 10 patients with central retinal vein occlusion was given desferrioxamine B (Desferal®) 1 g intramuscularly pro die for two weeks None of the patients developed hemorrhagic glaucoma The posthrombotic

Aus der Universitäts-Augenklinik Rostock – DDR
Direktor: Prof. Dr. med. habil. G. Pietruschka

ÜBER DEN MYOPISIERUNGSEFFEKT VON PILOCARPIN (1%), JESTRYL (DORYL) (1%) UND NEOESERIN (PROSTIGMIN) (3%) AUGENTROPFEN*)

VON

H. KERGER, W. PAUL und H. WILD

Jeder Augenarzt, der Glaukomkranke betreut, wird bei der konservativen Behandlung nicht selten mit dem Problem konfrontiert, dass unter Anwendung eines Miotikums der Augendruck zwar gut reguliert sein kann, gleichzeitig aber starke subjektive Beschwerden auftreten. Ein grosser Teil dieser unangenehmen Begleiterscheinungen der Miotika, insbesondere bei jugendlichen noch akkommodationsfähigen Patienten, geht auf eine transitorische Myopie zurück, die durch einen Krampf des Ziliarmuskels verursacht wird (*vom Hofe*). *Lohlein* wies darauf hin, dass bei Daueranwendung der Miotika die Störungen des Sehvermögens in manchen Berufen erhebliche Beeinträchtigung mit sich bringen und deshalb eine Indikation zur Operation darstellen können.

Die Aufmerksamkeit der hier mitgeteilten Untersuchungen gilt daher der Frage, in welchem Masse die gebräuchlichsten Miotika Pilocarpin, *Jestryl* (Doryl) und Neoeserin (Prostigmin) die Sehschärfe und damit Berufs- und Verkehrsfähigkeit (*Pietruschka*, *Spiecker*) beeinflussen.

Das Pilocarpin – Hauptalkaloid der Foliae Jaborandi des südamerikanischen Pilocarpus Strauches – wurde 18.. von *Weber* in die Glaukomtherapie eingeführt. Es handelt sich um ein Parasympathikomimetikum, das *in seiner* Struktur Beziehungen zum Azetylcholin und Muskarin aufweist. Chemisch besteht es aus einem Imidazol- und einem Furanonring, verbunden durch eine CH_2-

*) Auszugsweise vorgetragen auf der Tagung der Berliner Augenärztlichen Gesellschaft am 1. und … Dezember 1967.

Eingegangen am 1? Juli 1968

Wood D J A suggestion as to the cause of glaucoma following thrombosis of re al vein Britt J Ophthal *16* 428–424 1952

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ursacht dass die myopisierende Wirkung von Pilocarpin ½ %, 1%, 2% und in Substanz fast immer der Starke nach gleich war und sich nur in der Dauer unterschied Im allgemeinen liess sich der Akkommodationskrampf bei seinen Untersuchungen mit 3 bis 4 dpt auskorrigieren *Fanta* beobachtete bei der Untersuchung der Wirkungsweise von Pilocarpin an normalen Augen dass die Wirkung von Pilocarpin in verschiedenen Konzentrationen auf Augendruck Pupillengrosse und Akkommodationsmuskel nicht parallel geht auch keine Gesetzmassigkeiten bei verschiedener Refraktion und verschiedenem Alter zeigt

Wie auch von anderen Autoren (*Lewin* und *Guillery* *Berggren* *vom Hofe* u a) betont uberdauerte die Miosis den nachweisbaren Akkommodationskrampf *Berggren* der drei Manner im Alter von 13 26 und 37 Jahren untersuchte beschrieb nach 2%igen Pilocarpintropfen eine Myopie deren Grad in Relation zum Alter stand und deren Dauer 2 Std anhielt wahrend die Miosis langere Zeit bestand

Jestryl = Doryl (Carbachol Carbaminoylcholin Carcholin) 1933 von *K Velhagen* in der Glaukomtherapie eingefuhrt ist einer der aktivsten Cholinester (Karbamidsaurecholinester) mit einer protrahierten Azetylcholinwirkung (*Hauschild*) Es greift wie Pilocarpin direkt an der Muskelzelle an (*Leydhecker*) ausserdem soll es die Cholinesterase hemmen (*Leydhecker* *Leydhecker* *Dardenne* und *Helferich* *Lullies*) Andererseits betont *Hauschild* dass Doryl keinen cholinesterasehemmenden Effekt entfalte *R Thiel* erklarte den Wirkungsmechanismus des Doryls und anderer Cholinderivate mit ihrer Fahigkeit eine vermehrte Azetylcholinbildung zu bewirken Nach *Velhagen* verengt Doryl die menschliche Pupille errege jedoch die Akkommodation nicht sehr stark

Lommatzsch fand bei Untersuchungen am isolierten Ziliarmuskel von Mensch und Katze nach Carbaminoylcholineinwirkung eine hohere Kontraktionsgeschwindigkeit als nach Pilocarpinanwendung Bei Experimenten an Affen stellte *Tornquist* fest dass zur Erzielung einer Refraktionsanderung im Sinne einer Myopisierung hohere Dosen von lokal verabreichtem Pilocarpin und Carbachol notwendig waren als zum Auslosen einer Miosis

Beim Prostigmin handelt es sich um ein Dimethyl Karbaminsaureester von m Oxyphenyltrimethylammonium der etwas starker als Eserin reversibel die Cholinesterase hemmt (*Hauschild*) Neoeserin stellt das entsprechende Bromid dar *Possi* fand 1935 an Frosch Kaninchen normalen und glaukomatosen Menschenaugen dass das Prostigmin dem Pilocarpin und Eserin an drucksenkender und miotischer Wirkung uberlegen ist *Leydhecker* machte die Erfahrung dass Prostigmin oft starker drucksenkend wirke als Pilocarpin 2%ig jedoch seien Drucksenkungseffekt und Vertraglichkeit individuell sehr verschieden

Bauer stellte das Auftreten einer kurzfristigen Myopie bei Glaukompatienten

Brücke (*Hauschild*) Das Pilocarpin wirkt am Auge auf die Mm sphincter pupillae und ciliaris wobei der Angriffspunkt am Muskel selbst zu suchen ist (*Thiel Leydhecker*) Die Pilocarpinwirkung tritt gewissermassen neben den Nervenreiz und verstärkt seine Wirkung additiv (*Siebeck*) Unter der Pilocarpineinwirkung kommt es am Auge u a zu einer Beeinflussung der Akkommodation und der Pupillenweite *Lewin* und *Guillery* hoben hervor dass die Akkommodationsveränderungen nach Pilocarpin sich »mehr durch eine Annäherung des Fernpunktes auszeichnen« Sie beobachteten dass nach Eintraufelung von 1 bis 2 %igen Pilocarpintropfen der Fernpunkt so genahert wird dass er fast mit dem Nahpunkt zusammenfällt der ebenfalls näher heranruckt Bei ihren Untersuchungen an gesunden Augen verschieden alter Versuchspersonen verursachte Pilocarpin eine Fernpunktverlagerung von ca 2 2 bis 4 dpt die ihr Maximum nach 35 Min erreichte und etwa 50 bis 85 Min andauerte *Vom Hofe* befasste sich systematisch mit den unangenehmen Nebenwirkungen von Pilocarpin Er gelangte zu dem Ergebnis dass die Sehstorungen nach Pilocarpin auf eine durch einen Akkommodationskrampf hervorgerufene Myopie zurückgehen und sich durch Konkavgläser ausgleichen lassen Durch Vorsetzen von stenopäischen Blenden lässt sich beweisen dass die Schverschlechterung nicht durch die Miosis bedingt ist *Vom Hofe* beobachtete nach der Verabreichung von 3 Tropfen einer 2 %igen Pilocarpinlösung in den Bindehautsack eine passagere Myopie die nach ca 50 Minuten ihren Hohepunkt mit –1 5 dpt erreichte und nach eindreiviertel Stunden nicht mehr nachweisbar war Nach Abklingen der Myopisierung bestand lediglich eine leichte Verschleierung *Vom Hofe* stellte weiterhin fest dass der Nahpunkt sich nach der Pilocarpin Applikation mit dem Einsetzen der Sehstörung dem Auge nahert nach 3 bis 4 Stunden aber weiter vom Auge entfernt ist als es seiner ursprunglichen Lage entspricht erst nach neun bis zehn Stunden erreiche der Nahpunkt seine Ausgangsstelle wieder Dieses Phänomen wurde als geringe dem Akkommodationskrampf folgende Akkommodationsparese gedeutet die 3 bis 4 Stunden nach der Eintraufelung von Pilocarpin eintritt und eine Nahpunktverschiebung von zirka 1 cm bewirkt

Bei 1 %iger Pilocarpinlosung fand *vom Hofe* keine prinzipiell anderen Phanomene nur hielt die geringe Akkommodationsparese nicht so lange an und war ausserdem schwacher ausgeprägt *Vom Hofe* fielen bei der Untersuchung der Pilocarpinwirkung auf die Akkommodation jugendlicher Personen Unterschiede in bezug auf Dauer und Wirkungsgrad des Pilocarpins auf Er weist darauf hin dass auch Personen im hohen Alter nach Pilocarpin eine vorubergehende Myopie aufweisen konnen selbst wenn nur noch ein geringer Akkommodationsaufwand moglich ist zumal die Akkommodationsreste nicht immer gleich sind und nicht der *Donders*schen Kurve zu entsprechen brauchen

Fanta stellte bei seinen Untersuchungen an normalen Augen fest dass eine 1/4 %ige Pilocarpinlösung keinen nachweisbaren Akkommodationskrampf ver

Tabelle 1

Höhe des *Myopisierungseffektes* von Pilocarpin Augentropfen (1 %ig) unter Berücksichtigung des Lebensalters (149 Augen)

Lebensjahre	Gesamtzahl der untersuchten Augen	ohne Myopisierung	mit Myopisierung	Myopisierungseffekt in dpt			
				bis 1,0	1,25–2,0	2,25–3,0	3,25 und mehr
bis 20	6	4	2	1	1	–	–
21–30	17	2	15	5	3	3	4
31–40	38	15	23	10	5	2	6
41–50	43	24	19	5	12	2	–
51–60	45	38	7	6	1	–	–
Summe	149	83	66	27	22	7	10

bei einem Drittel länger als 90 Minuten an (Tab. 2). Erwartungsgemäss zeigt sich in Ausmass und Dauer der transitorischen Myopie eine Abhängigkeit von der Akkommodationsfähigkeit: im 5. und 6. Lebensjahrzehnt nimmt die Intensität des Myopisierungseffektes deutlich ab. Andererseits fällt auf, dass in der Altersgruppe bis zu 20 Jahren nur zwei von sechs Augen eine vorübergehende Kurzsichtigkeit aufweisen. Tabelle 3 lässt erkennen, dass Dauer und Ausmass

Tabelle 2

Dauer des Myopisierungseffektes in Minuten bei 66 Augen mit transitorischer Myopie durch Pilocarpin Augentropfen 1 %ig unter Berücksichtigung des Lebensalters

Lebensjahre	Anzahl der Augen mit transitorischer Myopie	Myopisierungseffekt abgeklungen			
		nach 30	nach 60	nach 90	nach über 90
bis 20	2	–	–	–	2
21 bis 30	15	1	2	5	7
31 bis 40	3	–	8	7	8
41 bis 50	19	1	6	9	3
51 bis 60	7	2	4	1	–
Summe	66	4	20	22	20

mittleren Alters nach 1 %igem Prostigmin fest *Weber* beobachtete dass d Wirkung von Prostigmin auf die Akkommodation nach 60 bis 80 Min en bereits wieder abgeklungen war *Junghannss* konnte keinen wesentlichen Einfluss von Prostigmin auf Tension und Akkommodation des normalen Au es feststellen

Im Rahmen unserer klinischen Möglichkeiten bot sich d e subjektive Refraktionsbestimmung als geeignete Untersuchungsmethode an Wie bei der normalen Glaukomtherapie üblich wurde 1 Tropfen des jeweiligen Medikamentes am sitzenden Patienten in den Bindehautsack verabreicht Die Höhe der transitorischen Myopie wurde 15 30, 60 90 120 Minuten nach Applikation des Medikaments mit der Methode der subjektiven Refraktionsbestimmung (*Snellen*-Tafel in 5 m Entfernung) ermittelt Refraktionsänderungen ab -0 5 dpt wurden als Myopisierungseffekt gewertet Nach Möglichkeit wurde vor der Verabreichung der Miotika die Refraktion skiaskopisch ermittelt Bei einem Teil der Glaukompatienten verbot sich aus verständlichen Gründen eine objektive Refraktionsbestimmung unter Anwendung von Mydriatika Unsere Untersuchungen erstreckten sich nur auf die Bestimmung der Fernpunktverlagerung Die Verlagerung des Nahpunktes blieb unberücksichtigt Das Untersuchungsgut setzte sich aus Glaukompatienten der Jahre 1965–1968 zusammen Die Probanden beiderlei Geschlechts befanden sich im Alter zwischen 14 und 60 Jahren Insgesamt gelangten 419 Untersuchungen die an 270 Augen von 143 Personen durchgeführt wurden zur Auswertung Patienten die an Krankheiten litten oder mit Medikamenten behandelt wurden die zu einer transitorischen Ametropie führen können (*Sachsenweger*) wurden von den Untersuchungen ausgeschlossen

Es wurden folgende in der konservativen Glaukomtherapie der Rostocker Universitäts Augenklinik häufig benutzten Medikamente auf ihren Myopisierungseffekt hin untersucht Pilocarpin (1 %ig) Jestryl (Doryl) (1 %ig) und Neoeserin (Prostigmin) Augentropfen (3 %ig) Wir verwandten für unsere Untersuchungen die handelsüblichen 1 %igen Jestryl (Doryl) Augentropfen der Firma Ankerwerk Rudolstadt und die 3 %igen Neoeserintropfen (Prostigmin) die von Isis Chemie Zwickau hergestellt werden Die verwendeten 1 % Pilocarpin Augentropfen fertigte uns die Zentralapotheke der Rostocker Medizinischen Fakultät (Leiter Ph R Dr *Freitag*) nach den Prinzipien des DAB 7 an

Der Myopisierungseffekt von 1 %igen Pilocarpin Augentropfen wurde an 149 Augen von 75 Patienten im Alter von 14–60 Jahren (Durchschnittsalter 42 2 Lebensjahre) untersucht (Tab 1–3) 66 Augen – 44 % – reagierten mit einer transitorischen Myopie (Tab 1) 39 von 66 Augen – zirka 59 % – wiesen eine passagere Myopie von mehr als 1 dpt auf vorzugsweise zu Lasten der Patienten im Alter von 21 bis 40 Jahren Bei etwa zwei Dritteln der Augen mit passagerer Myopie hielt diese nach Pilocarpin 1 % länger als eine Stunde

4 zeigt dass in ahnlicher Weise wie bei Pilocarpin 1 % bei uber der Halfte dieser durch Jestryl (Doryl) (1 %) myopisierten Augen die Myopie mehr als 1 dpt bei einem Sechstel mehr als 2 dpt betrug Auch hier wird die Gruppe der 21 bis 40 jahrigen am starksten von der transitorischen Myopie betroffen Wie auch bei Pilocarpin 1 % fallt auf dass nur wenige Patienten der ersten Altersgruppe eine transitorische Myopie aufweisen Bei uber 70 % der Augen (Tab 5) die auf Jestryl (Doryl) mit einer transitorischen Myopie reagierten hielt die Sehverschlechterung langer als 1 Stunde bei immerhin noch zirka 37 % langer als 90 Minuten an Auch bei Jestryl (Doryl) ergibt sich zwischen Dauer und Ausmass der passageren Myopie ein annahernd proportionales Verhaltnis (Tab 6)

Die Tabellen 7 bis 9 geben Auskunft uber den Myopisierungseffekt von Neoeserin (Prostigmin) Augentropfen (3 %) der an 75 Augen von 41 Patienten im Alter von 20-60 Jahren (Durchschnittsalter 44 8 Jahre) getestet wurde Lediglich 14 dieser 75 Augen – zirka 19 % – boten eine transitorische Myopie die nur viermal die Hohe von 1 dpt uberstieg Eine passagere Myopie uber 2 dpt wurde bei unseren Untersuchungen unter Anwendung von Neoeserin (Prostigmin) 3 % in keinem Falle beobachtet Der Tab 8 lasst sich entnehmen dass bei allen Augen mit transitorischer Myopie nach *Neoeserin (Prostigmin)* 3 % diese langer als 30 Minuten andauerte beim uberwiegenden Teil bereits nach einer Stunde abgeklungen war jedoch bei drei Augen langer als 90 Minuten fortbestand Wie aus Tabelle 9 ersichtlich erreichte die Myopisierung dieser drei Augen die unter Neoeserin (Prostigmin) 3 % *ermittelten* Maximalwerte

Tabelle 5

Dauer des Myopisierungseffektes in Minuten bei 76 Augen mit transitorischer Myopie durch Jestryl Augentropfen (1 %ig) unter Berucksichtigung des Lebensalters

Lebensjahre	Anzahl der Augen mit transitorischer Myopie	Myopisierungseffekt abgeklungen			
		nach 30	nach 60	nach 90	nach uber 90
bis 20	3	–	–	3	–
21 bis 30	1	2	3	4	3
31 bis 40	36	–	6	11	19
41 bis 50	17	–	3	8	6
51 bis 60	8	1	4	2	1
Summe	6	3	16	28	29

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Tabelle 3
Beziehungen zwischen Höhe und Dauer des Myopisierungseffektes von Pilocarpin (1 %ig) bei 66 Augen

Myopisierungseff. abgeklungen nach	Höhe des Myopisierungseffektes in dpt				
	bis 1,0	1,25 – 2,0	2,25 – 3,0	3,25 und mehr	Summe
30	4	–	–	–	4
60	17	3	–	–	20
90	5	12	5	–	22
über 90	1	7	2	10	20
Summe	27	22	7	10	66

des Myopisierungseffektes von Pilocarpin 1 % in einem annähernd proportionalen Verhältnis zueinander stehen.

Ähnliche Ergebnisse wie bei Pilocarpin Augentropfen (1 %) ergaben sich bei der Untersuchung des Myopisierungseffektes von Jestryl (Doryl) Augentropfen (1 %). Bei 195 Augen wurde die transitorische Myopie unter der Behandlung mit diesem Medikament ausgemessen. Die 98 untersuchten Patienten befanden sich im Alter von 16 bis 60 Jahren (Durchschnittsalter 41,8 Jahre). 76 Augen – zirka 39 % – wiesen eine Myopisierung auf (Tab. 4). Tab.

Tabelle 4
Myopisierungseffekt von Jestryl (Doryl) Augentropfen (1 %ig) unter Berücksichtigung des Lebensalters (195 Augen)

Lebensjahre	Gesamtzahl der untersuchten Augen	ohne Myopisierung	mit Myopisierung	Myopisierungseffekt in dpt			
				bis 1,0	*1,25 – 2,0*	*2,25 – 3,0*	*3,25 und mehr*
bis 20	8	5	3	3	–	–	–
21 – 30	17	5	12	5	4	1	2
31 – 40	58	22	36	12	10	8	6
41 – 50	53	36	17	9	4	4	–
51 – 60	59	51	8	8	–	–	–
Summe	195	119	76	37	18	13	8

4 zeigt dass in ahnlicher Weise wie bei Pilocarpin 1 % bei uber der Halfte dieser durch Jestryl (Doryl) (1 %) myopisierten Augen die Myopie mehr als 1 dpt bei einem Sechstel mehr als 2 dpt betrug Auch hier wird die Gruppe der 21 bis 40 jahrigen am starksten von der transitorischen Myopie betroffen Wie auch bei Pilocarpin 1 % fallt auf dass nur wenige Patienten der ersten Altersgruppe eine transitorische Myopie aufweisen Bei uber 70 % der Augen (Tab 5) die auf Jestryl (Doryl) mit einer transitorischen Myopie reagierten hielt die Sehverschlechterung langer als 1 Stunde bei immerhin noch zirka 37 % langer als 90 Minuten an Auch bei Jestryl (Doryl) ergibt sich zwischen Dauer und Ausmass der passageren Myopie ein annahernd proportionales Ver haltnis (Tab 6)

Die Tabellen 7 bis 9 geben Auskunft uber den Myopisierungseffekt von Neoeserin (Prostigmin) Augentropfen (3 %) der an 75 Augen von 41 Patienten im Alter von 20–60 Jahren (Durchschnittsalter 44 8 Jahre) getestet wurde Lediglich 14 dieser 75 Augen – zirka 19 % – boten eine transitorische Myopie die nur viermal die Hohe von 1 dpt uberstieg Eine passagere Myopie uber 2 dpt wurde bei unseren Untersuchungen unter Anwendung von Neoeserin (Prostigmin) 3 % in keinem Falle beobachtet Der Tab 8 lasst sich entnehmen dass bei allen Augen mit transitorischer Myopie nach Neoeserin (Prostigmin) 3 % diese langer als 30 Minuten andauerte beim uberwiegenden Teil bereits nach einer Stunde abgeklungen war jedoch bei drei Augen langer als 90 Minuten fortbestand Wie aus Tabelle 9 ersichtlich erreichte die Myopisierung dieser drei Augen die unter Neoeserin (Prostigmin) 3 % *ermittelten Maximal* werte

Tabelle 5

Dauer des Myopisierungseffektes in Minuten bei 76 Augen mit transitorischer Myopie durch Jestryl Augentropfen (1 %ig) unter Berucksichtigung des Lebensalters

Lebensjahre	Anzahl der Augen mit transitorischer Myopie	Myopisierungseffekt abgeklungen			
		nach 30	nach 60	nach 90	nach uber 90
bis 20	3	–	–	3	–
21 bis 30	12	2	3	4	3
31 bis 40	36	–	6	11	19
41 bis 50	17	–	3	8	6
51 bis 60	8	1	4	2	1
Summe	6	3	16	23	29

Tabelle 6

Beziehungen zwischen Höhe und Dauer des Myopisierungseffektes von Jestryl (Doryl) Augentropfen (1 %ig) bei 76 Augen

Myopisierungseffekt abgeklungen nach	Höhe des Myopisierungseffektes in dpt				
	bis 1,0	1,25 – 2,0	2,25 – 3,0	3,25 und mehr	Summe
30	3	–	–	–	3
60	11	3	2	–	16
90	19	7	2	–	28
über 90	4	8	9	8	29
Summe	37	18	13	8	76

Tabelle 7

Höhe des *Myopisierungseffektes* von Neoeserin Augentropfen (3 %ig) unter Berücksichtigung des Lebensalters (75 Augen)

Lebensjahre	Gesamtzahl der untersuchten Augen	ohne Myopisierung	mit Myopisierung	Myopisierungseffekt in dpt			
				bis 1,0	1,25 – 2,0	2,25 – 3,0	3,25 und mehr
bis 20	2	–	2	–	2	–	–
21 – 30	4	4	–	–	–	–	–
31 – 40	15	10	5	4	1	–	–
41 – 50	29	25	4	3	1	–	–
51 – 60	25	22	3	3	–	–	–
Summe	75	61	14	10	4	–	–

Die vorliegenden Ergebnisse zeigen, dass nach lokaler Anwendung von Pilocarpin (1 %) und Jestryl (Doryl) Augentropfen (1 %) in zirka 11 bzw. zirka 39 % der von uns untersuchten Augen vornehmlich zu Lasten der jüngeren Patienten unter den geschilderten Untersuchungsbedingungen eine transitorische Myopie zustande kam (Tab. 10). Das bedeutet, dass bei einem nicht unerheblichen Teil der mit diesen genannten Medikamenten behandelten Glaukompatienten eine Herabsetzung des Sehvermögens auf die Hälfte und weniger und damit eine Beeinträchtigung der Verkehrs- und je nach Tätigkeit

Tabelle 8

Dauer des Myopisierungseffektes in Minuten bei 14 Augen mit transitorischer Myopie durch Neoeserin Augentropfen (1 %ig) unter Berücksichtigung des Lebensalters

Lebensjahre	Anzahl der Augen mit transitorischer Myopie	Myopisierungseffekt abgeklungen			
		nach 30	nach 60	nach 90	nach über 90
bis 20	2	–	–	–	2
21 bis 30	–	–	–	–	–
31 bis 40	5	–	5	–	–
41 bis 50	4	–	2	1	1
51 bis 60	3	–	2	1	–
Summe	14	–	9	2	3

Tabelle 9

Beziehungen zwischen Höhe und Dauer des Myopisierungseffektes von Neoeserin (Prostigmin) Augentropfen (3 %ig) bei 14 Augen

Myopisierungseffekt abgeklungen nach	Höhe des Myopisierungseffektes in dpt			
	bis 1,0	1,05–2,0	mehr als 2,0	Summe
30	–	–	–	–
60	8	1	–	9
90	2		–	2
über 90	–	3	–	3
Summe	10	4	–	14

auch der Berufsfähigkeit für mindestens eine Stunde resultiert. In diesem Zusammenhang sei auf die Feststellung *Pietruschkas* hingewiesen, dass Glaukompatienten mit miotikabedingter transitorischer Myopie untauglich zum Führen von Kraftfahrzeugen sind.

Beim Vergleich der drei erprobten Miotika stellt es sich heraus, dass Neoeserin (Prostigmin) 3 % unter den geschilderten Untersuchungsbedingungen mit

Tabelle 6

Beziehungen zwischen Höhe und Dauer des Myopisierungseffektes von Jestryl (Doryl) Augentropfen (1 %ig) bei 76 Augen

Myopisierungseffekt abgeklungen nach	Höhe des Myopisierungseffektes in dpt				
	bis 1,0	1,25–2,0	2,25–3,0	3,25 und mehr	Summe
30	3	–	–	–	3
60	11	3	2	–	16
90	19	7	2	–	28
über 90	4	8	9	8	29
Summe	37	18	13	8	76

Tabelle 7

Höhe des *Myopisierungseffektes* von Neoeserin Augentropfen (3 %ig) unter Berücksichtigung des Lebensalters (75 Augen)

Lebensjahre	Gesamtzahl der untersuchten Augen	ohne Myopisierung	mit Myopisierung	Myopisierungseffekt in dpt			
				bis 1,0	1,25–2,0	2,25–3,0	3,25 und mehr
bis 20	2	–	2	–	2	–	–
21–30	4	4	–	–	–	–	–
31–40	15	10	5	4	1	–	–
41–50	29	25	4	3	1	–	–
51–60	25	22	3	3	–	–	–
Summe	75	61	14	10	4	–	–

Die vorliegenden Ergebnisse zeigen, dass nach lokaler Anwendung von Pilocarpin (1 %) und Jestryl (Doryl) Augentropfen (1 %) in zirka 44 bzw. zirka 39 % der von uns untersuchten Augen vornehmlich zu Lasten der jüngeren Patienten unter den geschilderten Untersuchungsbedingungen eine transitorische Myopie zustande kam (Tab. 10). Das bedeutet, dass bei einem nicht unerheblichen Teil der mit diesen genannten Medikamenten behandelten Glaukompatienten eine Herabsetzung des Sehvermögens auf die Hälfte und weniger und damit eine Beeinträchtigung der Verkehrs- und je nach Tätigkeit

haben *Hess* und *van Heuven* nahmen aufgrund entoskopischer Untersuchungen einen Einfluss der Miotika auf die Netzhautzirkulation an *H Hager* ist der Meinung dass die trotz Ausgleich der Refraktionsanderung fortbestehenden Sehstorungen u a durch rasch wechselnde Kontraktionen des gereizten Ziliar muskels hervorgerufen werden Es liesse sich u F vorstellen dass diese rasch wechselnden Kontraktionen nicht kreissymmetrisch erfolgen sondern nur einige Sel toren des Ziliarmuskels betreffen und sich in Form eines akkommodativen Astigmatismus wie er von *Mut e* beschrieben wird aussert Anhaltspunkte dafur fanden sich bei unseren Untersuchungen Entsprechend der Feststellung von *vom Hofe* und *Allen* dass die Restakkommodation alter Menschen hoher ist als gewohnlich angenommen wird konnten auch wir bei Patienten im sechsten Lebensdezennium haufiger eine passagere Kur sichtigkeit nach Miotika registrieren als wir anfanglich erwartet hatten Andererseits fallt bei den vorliegenden Untersuchungsergebnissen auf dass nur relativ wenig Patienten der jungsten Altersgruppe auf die drei Miotika mit einer vorubergehenden Kurzsichtigkeit reagierten Wegen des geringen Umfanges der *Untersuchungen* sei diese Erscheinung lediglich vermerkt Verallgemeinernde Schlussfolgerun gen erscheinen unangebracht eine Erklarung des Phanomens kann nicht gege ben werden

Wie auch *vom Hofe* mochten wir die Tatsache dass es bei Versuchspersonen gleichen Alters und gleicher Refraktion in einem Falle zur Myopisierung kommt im anderen Falle jedoch keine Beeinflussung des Akkommodations apparates erfolgt am ehesten mit einer Verschiedenheit der vegetativen Aus gangslage erklaren *Frey* fasste die Ergebnisse zahlreicher Untersuchungen da hingehend zusammen dass der Reizerfolg an vegetativen *Nerven weitgehend* vom Zustand des innervierten Organs abhangig ist Bei parasympathischer Disposition kann eine sympathische Reizung wie ein Vagusreiz wirken und um gekehrt

Die experimentellen Forschungsergebnisse insbesondere von *Meesmann Siebeck* und *Monje* haben gezeigt dass der Ziliarmuskel sowohl vom Para sympathikus als auch vom Sympathikus innerviert wird Dadurch *zeichnen sich* Moglichkeiten ab durch geeignete Kombinationen von sympathiko und parasympathikomimetischen Augentropfen eine ausreichende Drucksenkung unter Umgehung der transitorischen Myopie zu erreichen In der Universitats Augenklinik Rostock *wurden in dieser Richtung Versuche mit* Kombinations praparaten in Form von Pholedrin Pilocarpin Mischtropfen unternommen Es liess sich nachweisen dass durch Anwendung von Neoeserin (Frostigmin) Au gentropfen den genanten Mischtropfen und von linksdrehenden *Adrenalin* Fraparaten allein *(Langhol)* – oder in Kombination *mit* Miotika *(Fechner)* – *eine transitorische* Myopie vermieden oder in Grenzen gehalten werden kann so dass in den letzten Jahren der Myopisierungseffekt *in* keinem Falle eine Indikation zur drucksenkenden Operation darstellte

Tabelle 10

Gegenüberstellung des Myopisierungseffektes von Pilocarpin (1 %ig), Jestryl (1 %ig) und Neoeserin (3 %ig) Augentropfen hinsichtlich der Höhe der transitorischen Myopie

Medikament	ohne Myopisierung	mit Myopisierungseffekt in dpt				
		bis 1,0	1,25–2,0	2,25–3,0	3,25 und mehr	Summe
Pilocarpin 1 %ig	83 = 56 %	27	22	7	10	66 = 44 %
Jestryl 1 %ig	119 = 61 %	37	18	13	8	76 = 39 %
Neoeserin 3 %ig	61 = 81 %	10	4	–	–	14 = 19 %

zirka 19 % den geringsten Myopisierungseffekt auslöste, sowohl in bezug auf Höhe als auch Dauer (Tab. 10). Die Differenz zwischen der myopisierenden Wirkung von Pilocarpin 1 % (zirka 44 %) und Neoeserin (Prostigmin) 3 % (zirka 19 %) auf der einen Seite und von Jestryl (Doryl) 1 % (zirka 39 %) und Neoeserin (Prostigmin) 3 % (zirka 19 %) auf der anderen Seite erwies sich bei Anwendung des χ Testes unter Zugrundelegung einer Irrtumswahrscheinlichkeit von 0,3 % als signifikant. Auf diese Weise werden die klinischen Erfahrungen bestätigt. Kam es bei jugendlichen Glaukompatienten nach Verabreichung von Pilocarpin oder Jestryl (Doryl) zu subjektiven Beschwerden im Sinne einer transitorischen Myopie, so konnte in vielen Fällen durch Anwendung von Neoeserin (Prostigmin) eine ausreichende Drucksenkung ohne störenden Myopisierungseffekt erzielt werden. Es soll nicht verschwiegen werden, dass wie auch andere Autoren (*Bauer, Junghanuss, Weber*) mitteilen, von einigen Patienten unter der Einstellung mit Neoeserin (Prostigmin) über Kopfschmerzen geklagt wird. Diese Zephalgien werden auf einen Krampf des Sphincter pupillae zurückgeführt. Sehr oft klingen die Beschwerden durch Gewöhnung in wenigen Tagen ab. Es ergab sich kein signifikanter Unterschied zwischen dem Myopisierungseffekt von Pilocarpin 1 % (zirka 44 %) und Jestryl (Doryl) 1 % (zirka 39 %). Eine Erklärung für die unterschiedliche Wirkungsintensität von Pilocarpin und Jestryl (Doryl) einerseits und Neoeserin (Prostigmin) andererseits auf den Ziliarmuskel könnte vielleicht in den unterschiedlichen Angriffsmechanismen dieser Pharmaka zu suchen sein.

In unserem Patientengut befanden sich auch einzelne Personen, bei denen sich die Sehverschlechterung nach Miotika nicht restlos durch sphärische Minusgläser ausgleichen liess, ähnlich wie es *Hess* und *vom Hofe* beschrieben

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Zusammenfassung

Der Myopisierungseffekt der Miotika Pilocarpin (1 %), Jestryl (Doryl) (1 %) und Neoeserin (Prostigmin) (3 %) wurde an 270 glaukomkranken Augen von 143 Personen im Alter zwischen 14 und 60 Jahren untersucht. Es stellte sich heraus, dass das Ausmass der transitorischen Myopie bei Pilocarpin und Jestryl (Doryl) deutlich höher als bei Neoeserin (Prostigmin) war.

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COMPLICATIONS FOLLOWING EYE TREATMENT WITH ^{90}Sr APPLICATOR

BY

ERIK LINNÉR and BENGT ROSENGREN

Ophthalmic treatment with β particles from a ^{90}Sr ^{90}Y source has been described by among others *Fridell et al* (1950) *Kaae* (1954) *Merriam* (1955) and *Lederman* (1956 1957 1961) Such treatment was deemed ideal for superficial affections when it was desired to achieve a high dose to the bulb without causing undesirable radiation effects in the internal parts of the eye

Disorders that lend themselves to this treatment include growth of vessels into the cornea pterygia associated with unspecific infections and tuberculous sclerokeratitis Other conditions are conjunctivitis (which also may affect the bulbar conjunctiva) naevus formations and tumours mostly malignant melanomata but also others such as papilloma Bowen s disease and conjunctival carcinoma

Apart from early side effects in the form of transient conjunctivitis accompanying the primary reaction to irradiation the aforementioned workers reported late side effects in the form of cataract and conjunctival atrophy

Moreover *Wilson* (1952) demonstrated corneal lesions after the high dose of 35 000 rads *Merriam* (1955) too reported atrophy of the iris after a high dose 20 000–30 000 rads

Several workers have cautioned against late side effects especially cataract and *Lederman* (1956) proposed that no more than 5000 rads should be administered per field Other authors such as *MacDonald et al* (1955) and *Merriam* (1955) have concurred in these warnings *Merriam* even suggesting that the surface dose per field should be limited to 2000–3000 rads

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Material and Methods

In the following we wish to present the results of treatment of 22 patients examined in the Eye Department and treated in the Radiotherapeutic Department Sahlgrenska sjukhuset Goteborg The diagnoses are given in Table 1

Treatment was effected with a ^{90}Sr-^{90}Y applicator supplied by Tracerlab Inc The active diameter is 6 mm and in use the dosage output was 90–76 rads per second According to the graph supplied by the manufacturer of the instrument the depth dose at 1 mm is 50 % at 2 mm 25 % at 3 mm 13 % and at 4 mm it is 6 % of the surface dose

15 patients received irradiation to a single field per eye 4 towards two fields in the same eye 2 towards three field and 1 towards 5 fields in the same eye (corresponding to approximately half the circumference at the limbus) The daily dose per field ranged from about 1000 rads up to 2000 rads and the total dose from some 3000 rads up to a maximum of around 18 000 rads On account of overlapping the maximum total dose administered to the patient with 5

Table 1

Diagnosis	No of patients	No of Fields treated per eye	Max dose in rads	No of patients improved	Complications
Vessels growing into transplantated cornea	1	1	6[illegible]00	–	–
Pterygium		1–3	5000–[illegible]0 000	1	–
Conjunctivitis	1	3	9600	1	–
Conjunctivitis vernalis	1	[illegible]	7[illegible]00	1	–
Keratitis	[illegible]	1–[illegible]	[illegible]000–16 000	1	–
Episcleritis	1	1	2[illegible]00	1	–
Corrosive lesion	1	1	6400	–	–
Epithelial growth into anterior chamber	[illegible]	1	3[illegible]00–7400	1	–
Naevi	7	1–2	[illegible]000–18 000	6	–
Malignant melanoma	3	1–[illegible]	16 000–20 000	1	–
Eyecancer	1	[illegible]	30 000	1	cataract

fields treated in the same eye was about 30 000 rads Numbers of fields per eye and maximal doses are also specified in Table 1

The patients underwent a complete ophthalmic examination before the treatment series and have since been seen again at varying intervals Of the patients treated 12 have been followed for more than 5 years 7 for 5 to 8 years and the remaining 3 for shorter periods In 1965 5 patients were re-examined and had their intraocular pressure measured This was 1-11 years after they had been treated and had received maximum doses of 5000-18000 rads (Table 2)

Results

As appears from Table 1 irradiation had beneficial effects on the signs and symptoms in 14 cases 6 of these patients felt completely cured A patient with malignant melanoma was enucleated 2 patients had undergone postoperative treatment 1 after excision of a conjunctival naevus and 1 after keratoplasty 13 patients have various persisting troubles due to teleangiectatic formations and ingrowing vessels The patient receiving irradiation to 5 fields around half the limbic circumference has developed cataract Neither cataract nor elevated intraocular pressure have supervened in the other patients At the follow up examination of 5 patients in 1965 no significant pressure elevation was recorded although a patient who had received 18 000 rads a year previously had higher pressure (19 7 mm Hg) in the treated than in the untreated eye (15 mm Hg) but the former pressure was not abnormally high

Table 2
Intraocular pressure at follow up 1965

Born	Treated	Irradiated eye P	Irradiated eye C	Not irradiated eye P_o	Not irradiated eye C	No of Fields treated	Max dose in rads
1948	1957	11 2	0 48	10 7	0 56	3	10 000
1947	1964	19	0 33	15 2	0 50	1	18 000
1920	1963	9 4	0 25	9 8	0 34	1	18 000
1915	1954	16 3	0 15	15 0	0 15	1	3 000
1951	1960	15 9	0 38	15 2	0 32	1	000

P_o stands for intraocular pressure in mm Hg C stands for facility of outflow

Discussion

Several previous workers have reported cataract after exposure to ionizing radiation for example *Poppe* (1942) who described animal experiments *Quist* and *Zachau Christiansen* (1959) who observed cataract in children after radio therapy (as did *Notter et al* 1966) and *Merriam* (1955) as well as *MacDonald et al* (1955) both of whom made similar observations after β therapy *Kumatori et al* (1965) reported cataract after irradiation from radioactive fallout

The results of animal experiments are not always applicable to clinical work Thus rabbits have a more radiosensitive lens than man and so get cataract more readily Young subjects are more sensitive than older ones (*Merriam* and *Focht* 1957)

Merriam and *Focht* (1957) stated with regard to radiation doses that a cataract may develop after radium or X ray therapy with a single dose of about 200 rads or after divided doses totalling 400 rads over a period of 1–3 months According to a preliminary report by *Notter et al* (1966) on radiation induced cataracts after radium therapy for haemangioma in children, minimal cataracts could be found in the dose interval 250–350 rads and dense cataracts from 550–1000 rads cataract invariably developed after doses exceeding 1150 rads

When the field to be irradiated with a $^{90}Sr-^{90}Y$ applicator is situated over the corneal limbus it is impossible to avoid some stray irradiation of the lens particularly its equator Suppose the distance to the lens is at least 3 mm then the equator of the lens will receive about 14 % of the surface dose and at a distance of 2 5 mm the dose at the chamber angle can attain 18 % *MacDonald et al* (19 5) and *Merriam* (1955) both stated that 4000 rads to the surface could give 00 rads to the lens equator and hence entail a risk for cataract

In the series of previous workers irradiation was administered around a large part of the limbic circumference and various forms of fractionation were used *Thompson* (1964) however reported cases in which irradiation was not administered so extensively and where there were no early or late side effects

Moreover published series have largely consisted of cases of corrosive injuries to the eye and the corrosion may have promoted the development of chan es that were interpreted as side effects of irradiation

When treating single fields we have in 6 cases given as much as 10 000–18 000 rads without cataract or elevated intraocular pressure yet having developed (Table 1) These manifestations generally set in within 2 years after irradiation according to the literature and therefore we are unable to confirm the observation that it is inadvisable to exceed 3000–4000 rads per field

In of our patients indeed up to 600 rads were given to each of two well separated fields in the same eye without any complications arising

When neighbouring fields are irradiated there is great risk of overlapping

as ocular fields are difficult to reproduce And cataract did develop in one case in which half the limbic circumference was treated in 5 fields with a maximal dose to overlapping portions of about 50 000 rads

The irradiation dose should be reduced substantially when neighbouring fields are treated and there is risk of overlapping If the treated region comprises half or more of the circumference at the limbus a further reduction is advisable according to the experiences of *Merriam* and *MacDonald et al* the dose then preferably not exceeding 3000–4000 rads per field

Interestingly with very soft radiation it is usual to ignore the volume dose but in a sensitive tissue like the lens the volume dose in a geometrically small region can become important and then the relative volume dose with ^{90}Sr–^{90}Y β irradiation may readily acquire cataractogenic significance

Summary

22 patients were irradiated with a ^{90}Sr–^{90}Y ophthalmic applicator Complications in the form of cataract were only noted in one case where 5 fields in one eye were irradiated with a maximum dose in overlapping areas of about 50 000 rads Single fields given up to 15 000 rads or two separate fields given 4000 rads each in one eye did not course cataract

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EXCITATION-INHIBITION ANOMALIES OF THE EXTRA OCULAR MUSCLES, ELECTROMYOGRAPHIC OBSERVATIONS

BY

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The electromyography (EMG) of a normal extraocular muscle in characterized by moderate electrical activity with the eye in the primary position progressively increasing electrical activity in the direction of its field of action and progressively decreasing activity, sometimes up to complete electrical silence with the eye moving in the antagonistic direction (*Bjork* 1954)

EMG evidence of an interplay of excitation (increase of activity) and inhibition (decrease of activity) between agonistic and antagonistic extraocular muscles is in accordance with the basic law of ocular motility that excitation of one group om muscles is closely associated with inhibition of the contralateral group

As some disorders of the ocular motility may be related to a disturbance of this delicate reciprocal mechanism we carried out EMG studies in such cases for further clarification The results which are presented here will be discussed in the light of their clinical significance

Method and Technique

The EMG examination was carried out on a two channel apparatus provided with mnemoscopic unit filming camera and loud speaker linked to a digital

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computer of average transients provided with analog to digital converter for duration and amplitude analysis Only coaxial needle electrodes were used Each patient underwent simultaneous EMG examination of two directly antagonistic extraocular muscles selected according to their clinical condition During the investigation the electrodes were relocated at least three times in order to ascertain their position within the body of the muscle and to provide sufficient information for averaging the EMG recordings

The technique of examination was as follows the patient was directed to first gaze in front of him (primary position) and then to follow a slowly moving object in the field of action of each of the two antagonistic muscles This procedure was repeated a number of times for each new location of the electrodes The degree of increase and decrease of electrical activity was related to the actual position of the eveglobe and the duration and amplitude of the action potentials were analyzed

Case Reports

Of the fourteen cases with a Duane s retraction syndrome which were examined one was chosen as an illustrative example

Case 1 A 19 year old male with congenital squint and watering of the right eye while eating The ophthalmological examination showed a visual acuity of 6/6 in each eye and mild exotropia in the primary position On dextroversion severe paresis of the Rt lateral rectus was apparent, accompanied by widening of the palpebral fissure the Lt medial rectus was mildly paretic with slight retraction of the eyeglobe On levoversion the Lt lateral rectus and Rt medial rectus were moderately paretic the right eyeglobe retracted and the palpebral fissure narrowed The near point of convergence was 25 cm Head turn to the right was noted No other ocular abnormalities were observed

EMG of the Rt lateral and medial recti was carried out. The medial rectus exhibited normal parameters with the eye in the primary position duration 1 15 ± 0 07 m sec amplitude 410 ± 35 micro V and full interference pattern on adduction the amplitude increased to an average of 450 micro V while on attempted abduction a decrease of electrical activity was obvious The lateral rectus also exhibited normal EMG parameters in mid position duration 1 10 ± 0 06 m sec amplitude 440 ± 40 micro V and a full interference pattern (Fig 1) On attempted abduction the amplitude showed a clear decrease to an average of 200 – 250 micro V (Fig 2) As the eye slowly moved in adduction, a gradual increase of the amplitude of the action potentials was apparent it attained upon maximal adduction an average of 400 micro V (Fig 3) This was a typical EMG paradoxic pattern and was observed on repeated examinations

A patient with dystrophic myotonia and a similarly abnormal EMG recording from one extraocular muscle is discussed in the following case

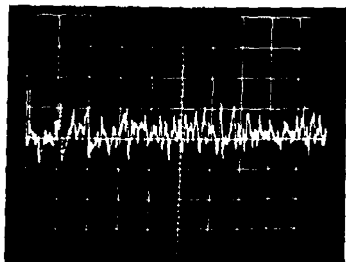


Fig 1

Case 1 EMG of the Rt lateral rectus muscle with the eye in mid position Calibration 400 micro V 5 m sec per square Full interference pattern may be observed Duration analysis 1 10 ± 0 06 m sec amplitude analysis 440 ± 40 micro V

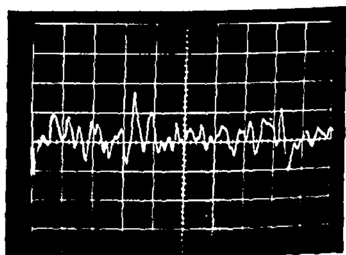


Fig 2

Case 1 EMG of the Rt lateral rectus muscle with eye in attempted abduction Calibration 200 micro V 3 m sec per square An obvious decrease of amplitude is apparent The other parameters are normal

Case 2 A 58 year old male with a history of weakness of the four extremities and mild difficulty in swallowing for the past three years and diplopia for the past two months All the symptoms were accentuated by cold weather Physical examination

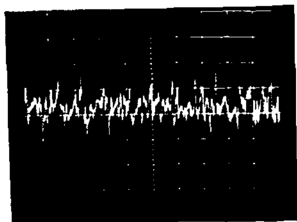


Fig 3

Case 1 EMG of Rt lateral rectus muscle with the eye in adduction Calibration 400 micro V 5 m sec per square Compared with Fig 2 a marked increase of amplitude is obvious The other parameters are normal

revealed weakness of the facial and limb muscles accompanied by mild atrophy especially of the temporal muscles (hatchet face) Mechanical myotonus was not found Percussion of various muscles did not elicit knots or wave like fasciculations Testicular atrophy was present Ocular examination revealed a visual acuity of 6 9 in each eye The Hess chart demonstrated mild paresis of the Lt inferior rectus Sub capsular opacities of the lens were present in both eyes No other ocular abnormalities were found

EMG of the gastrocnemius opponens pollicis and medial deltoid on the right side showed evidence of myopathy as manifested by decreased duration and amplitude in the presence of full interference pattern No EMG signs of a myotonic response were detected in the skeletal muscles EMG of the Lt inferior rectus (clinically mildly paretic) showed normal activity in its field of action duration 0 94 ± 0 05 m sec., amplitude 410 ± 45 micro V and full interference pattern when the patient was required to quickly shift the eyes from downward to upward gaze the muscle continued to show equally strong high frequency activity for a period of approximately 15 seconds followed by a gradual decrease of frequency and amplitude until almost complete electrical silence was apparent Continuous repetitions of the quick shift of gaze were followed by disappearance of this abnormal phenomenon, but after a brief period of rest the manoeuvre elicited the same EMG recording of persistent activity in the antagonistic field of motion If the shift of the eye from downward to upward gaze was carried out very slowly the inferior rectus muscle demonstrated the normal EMG of reciprocal inhibition The lateral and superior recti exhibited normal EMG recordings This type of abnormal EMG pattern, seen in the inferior rectus is characteristic of an EMG myotonic pattern

A different type of EMG pattern was observed in a patient suffering from the after effects of an injury to the orbit

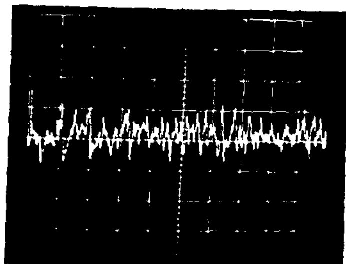


Fig 1

Case 1 EMG of the Rt lateral rectus muscle with the eye in mid position Calibration 400 micro V 5 m sec per square Full interference pattern may be observed Duration analysis 1 10 ± 0 06 m sec amplitude analysis 440 ± 40 micro V

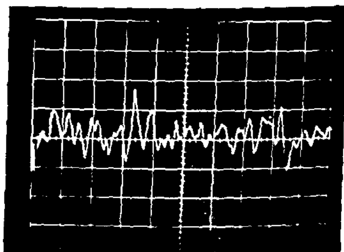


Fig 2

Case 1 EMG of the Rt lateral rectus muscle with eye in attempted abduction Calibration 200 micro V 3 m sec per square An obvious decrease of amplitude is apparent The other parameters are normal

Case 2 A 58 year old male with a history of weakness of the four extremities and mild difficulty in swallowing for the past three years and diplopia for the past two months All the symptoms were accentuated by cold weather Physical examination

of the eye in co contraction with the medial rectus The type of EMG recording encountered in these cases fits the criteria for a true paradoxic pattern because its basic mechanism is related to faulty or anomalous upper neurone innervation (control of the excitation inhibition reciprocal mechanism)

In Case 2 dystrophic myotonia the EMG demonstrated a normal pattern in the field of motion of the affected muscle However quick reversals of eye movement towards the field of action of its direct antagonist elicited a strong outburst of electrical activity followed by a series of outbursts of progressively lower amplitude and with wider intervals between them until almost complete electrical inactivity was observed This is a typical myotonic response similar in its characteristics to that observed in skeletal muscles On slow shift of gaze is was much less obvious tending to disappear on repetition of the same movement and to reappear after a brief period of rest The EMG recording seems to be similar to a paradoxic innervation but in contrast to it it occurs in rhythmic outbursts and tends to become exhausted

In Case 3 an abnormal EMG pattern was also obvious The incarcerated inferior rectus muscle was elongated upon attempted supraduction The EMG activity observed on upward gaze was most probably caused by a stretch reflex and secondary contracture of the overelongated muscle fibres This type of abnormal pattern is related to an essentially mechanical cause and once the obstacle is eliminated the EMG returns to normal We have previously observed this type of EMG pattern in a case of a blowout fracture of the orbital floor with dislocation of the eyeglobe (*Nawrat ki et al* 1968)

Although neuropathic and myopathic EMG patterns of the extraocular muscles have been well documented odd types of abnormal electrical activity related to reciprocal excitation inhibition mechanisms have not often been described When studied at all it has been mainly with regard to innervational (upper neurone) lesions Cases 2 and 3 exemplify similar types of abnormal electrical activity caused by muscular or myo neural disturbances of myotonic or mechanical origin we apply to these EMG patterns the term pseudo paradoxic in order to indicate their similarity to and differentiate them from a true paradoxic pattern which pertains to an upper neurone lesion

Summary

Three cases presenting atypical EMG patterns of extraocular muscles in their antagonistic fields of motion are presented

1) Duane s retraction syndrome in which the EMG demonstrated a true paradoxic pattern of excitation inhibition of upper motor neurone origin

Case 3 Two days prior to examination a 38 year old male was struck in the right eye by a fist during a brawl His main complaint was diplopia On examination, the visual acuity was 6/6 in each eye Periorbital swelling enophthalmos severe limitation of downward gaze and mild limitation of upward gaze were found Forced traction test showed impairment of passive downward and upward eye movement The X rays revealed a blowout fracture of the orbital floor

An EMG examination of the Rt inferior rectus muscle demonstrated on infraduction a full interference pattern with normal characteristics of the action potentials On supraduction instead of the expected inhibition strong electrical activity continued for 10–20 seconds If the patient held the eye in supraduction this abnormal EMG pattern was briefly evident with occasional decreased activity the amplitude was of the same magnitude (around 400 micro V) in each outburst of activity No sign of EMG fatigue was observed It should also be mentioned that the amplitude and frequency of firing were approximately equal in supra and infraduction indicating thereby maximal contraction of the muscle in both positions Surgical exploration revealed incarceration of the inferior rectus muscle in the fractured orbital floor A surgical muscle release was carried out and the orbit was repaired Six weeks after surgery the eye motility returned to normal and the diplopia completely disappeared. EMG investigation of the inferior rectus muscle at this time showed normal characteristics the excitation and inhibition were normal without evidence of increased activity upon eye motion in the antagonistic field of activity

Discussion

A paradoxic EMG pattern represents a striking abnormality of the excitation inhibition reciprocity mechanism of antagonistic muscles It is manifested by persistent muscle excitation in the antagonistic field of motion where decrease of activity should be obvious However although the EMG recordings appear to be similar a closer analysis of the parallel muscular activity may reveal different patterns of behaviour related to the original lesion

In Case 1 a Duane s retraction syndrome the affected muscle showed maximal and persistent electrical activity in the antagonistic field of motion while on attempting to move the eyeglobe in the muscle s field of motion no action potentials were elicited The EMG action potentials observed in the contralateral field of motion had normal parameters This would seem to indicate as has already been postulated (*Blodi et al* 1964 *Huber et al* 1964 *Orlowsky et al* 1962 *Papst et al* 1959 *Sato* 1960 and *Zauberman et al* 1967) that the basic lesion is in the upper motor neurone A possible explanation may be that fibers carrying impulses to the medial rectus nucleus also stimulate the abducens nucleus while on the other hand the fibers to the abducens nucleus (for abduction) are missing This hypothesis could explain the lack of EMG activity on abduction and the normal activity of the lateral rectus on adduction

of the eye in co contraction with the medial rectus The type of EMG recording encountered in these cases fits the criteria for a true paradoxic pattern because its basic mechanism is related to faulty or anomalous *upper neurone* innervation (control of the excitation inhibition reciprocal mechanism)

In Case 2 dystrophic myotonia the EMG demonstrated a normal pattern in the field of motion of the affected muscle However quick reversals of eye movement towards the field of action of its direct antagonist elicited a strong outburst of electrical activity followed by a series of outbursts of progressively lower amplitude and with wider intervals between them until almost complete electrical inactivity was observed This is a typical myotonic response similar in its characteristics to that observed in skeletal muscles On slow shift of gaze is was much less obvious tending to disappear on repetition of the same movement and to reappear after a brief period of rest The EMG recording seems to be similar to a paradoxic innervation but in contrast to it it occurs in rhythmic outbursts and tends to become exhausted

In Case 3 an abnormal EMG pattern was also obvious The incarcerated inferior rectus muscle was elongated upon attempted supraduction The EMG activity observed on upward gaze was most probably caused by a stretch reflex and secondary contracture of the overelongated muscle fibres This type of abnormal pattern is related to an essentially mechanical cause and once the obstacle is eliminated the EMG returns to normal We have previously observed this type of EMG pattern in a case of a blowout fracture of the orbital floor with dislocation of the eyeglobe (*Nawratki et al* 1968)

Although neuropathic and myopathic EMG patterns of the extraocular muscles have been well documented odd types of abnormal electrical activity related to reciprocal excitation inhibition mechanisms have not often been described When studied at all it has been mainly with regard to innervational (upper neurone) lesions Cases 2 and 3 exemplify similar types of abnormal electrical activity caused by muscular or myo neural disturbances of myotonic or mechanical origin we apply to these EMG patterns the term pseudo paradoxic in order to indicate their similarity to and differentiate them from a true paradoxic pattern which pertains to an upper neurone lesion

Summary

Three cases presenting atypical EMG patterns of extraocular muscles in their antagonistic fields of motion are presented

1) Duane's retraction syndrome in which the EMG demonstrated a true paradoxic pattern of excitation inhibition of upper motor neurone origin

2) Dystrophic myotonia, in which the EMG showed a myotonic response

3) A patient with a fracture of the orbital floor and muscle incarceration the overelongation of this muscle in supraduction caused EMG outbursts of activity out of its own field of motion due to a stretch reflex and a secondary contracture The latter two types of abnormal EMG electrical not of innervational origin, are referred to as "pseudo paradoxic

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PROTEIN CONTENT OF NORMAL HUMAN AQUEOUS HUMOUR IN VIVO

BY

U KRAUSE M D and V RAUNIO M D

The composition of the aqueous humour of the healthy human eye is relatively obscure Examination is hampered firstly by the minute quantity of the substance available for analysis – this difficulty however is today offset by sensitive methods of analysis – and secondly by the doubt that the sample analysed is completely primary aqueous humour The first problem has earlier been solved by combining several specimens (e g *Esser Hein ler* and *Pau* 1954) whereas the second problem still awaits solution

Many authors have contented themselves with autopsy studies (e g *François Rabaey* & *Evans* 1958 *Hemmingsen* & *Other* 1967) and considered that their results corresponded to conditions *in vivo* According to Adler (1965) however postmortem specimens are of no value

The protein content of the primary aqueous humour of the healthy human eye has been assigned values ranging from 5 to 50 mg/100 ml (e g., *Kronfeld* 1941 *Remky* 1956 *François* & *Rabaey* 1960) while the values quoted for plasmoid aqueous humour have been higher *Dieter* (1925) quoted 0 6–5 0 % (600–5000 mg/100 ml) *Wessely* (1903) 1 5–2 0 per cent (1500–2000 mg/100 ml) and *Adler* (1965) ~ per cent (,000 mg/100 ml) One criterion of purity for primary aqueous humour therefore would be the consistently low protein content of the aspirated specimen

Paracentesis is associated with a large number of sources of error some of which are recognized *Kronfeld Lin* & *Luo* (1941)) considered that the protein

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(5) The sample tube was later cut into lengths each containing a 10 cm fluid column (some 20 microlitres) of aqueous humour Several lengths were analysed for protein content by precision spectrophotometry (*Ewing* 1960) using Folin Ciocalteau s reagent (*Lowry Rosenbrough, Farr* and *Randall* 1951) The analysis was designed to require 5 microlitres of aqueous humour (? 5 cm fluid column) per protein determination

(6) The rate of aspiration was constant during each paracentesis The rates used in the different cases ranged from 0 4 to 1 3 microlitres/sec The volume of the sample drawn ranged from 130 to 368 microlitres

Material

The series consisted of 15 patients treated for amblyopia ex anopsia and or squint mean age 21 3 years The poorer eye was punctured

Results

The results are presented in Fig 3 A–B The abscissa indicates the volume of the specimen in microlitres and the ordinate the protein content in mg/100 ml

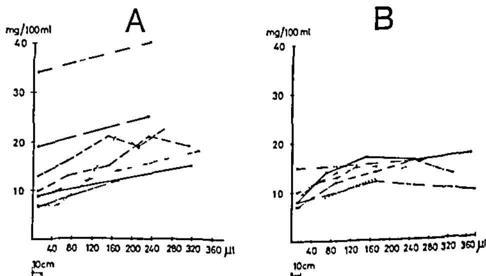


Fig 3 A B
Protein concentrations of normal aqueous humours mg/100 ml Volume of the specimen on the abscissa the first batch of specimen on the left in both A and B

for the corresponding length of 10 cm (20 microlitres) The first aspirated length of the specimen is on the left and the final length on the right in the figure The initial value of the total material averaged 11 2 mg % range 7–34 mg % The three highest values were from patients aged 49 years (= 34 mg/100 ml) 50 years (= 19 mg/100 ml) and 45 years (= 18 mg/100 ml) For each test subject the protein content showed a rising trend as the volume of the specimen increased yet the individual protein increases were not uniform the curve is uneven

If the volume of the anterior chamber is assumed to be 250 microlitres the specimens aspirated from eight patients exceeded the volume of this space The mean initial value for these patients was 8 9 mg/100 ml and by the time 250 microlitres had been aspirated the mean protein content calculated from the curves was 16 3 mg/100 ml The maximum protein value recorded for these eight patients was 23 mg/100 ml the recording was made after 270 microlitres had been aspirated

Discussion

The paracentesis of the anterior chamber is safe provided accurate sterility is observed The use of a paracentesis gun has not produced complications of any importance to the patient No lenticular lesions have been noted but attempts at avoiding them sometimes results in the tip of the needle being shot to the corneal stroma Immediately repeated paracentesis does not increase the reaction of the eye to the operation, but the specimen obtained has been discarded as valueless (cf above *Kronfeld Lin & Luo* 1941) If the needle is shot too deep the tip produces folds in the iris and a point like haemorrhage may follow In very severe uveitis and rubeosis of the iris small local haemorrhages of the anterior chamber have been noted during aspiration On the day following paracentesis the healthy eye shows a weak aqueous flare and/or *a few cells By the* second day the situation is again completely normal In iritic eyes descemetitis has occurred around the puncture but it has disappeared within a couple of days

Serial photographs taken during paracentesis show that the bulb *is scarcely* deformed during the puncture The speed the paracentesis needle *immediately* acquires reduced the trauma considerably The greatest advantage of this equipment the present authors found was the small trauma which from one puncture to another continues to be of *approximately* the same magnitude

Contraindications to paracentesis with a gun are a low anterior chamber and advanced rubeosis of the iris

The effect of topical anaesthetics selected at random on the protein conte·t has not been analysed but efforts were made to avoid sources of error by effecting the paracentesis ½–1 min after anaesthesia By the end of th aspiration the anaesthetic had already had time to produce adverse effects and consequently the potential error was greater The literature contains information on anaesthetics which raise the protein content considerably more than was the case in the present series The present results therefore were interpreted to indicate both a small puncture trauma and slight pharmacological effect of topical anaesthesia on the dynamics of the aqueous humour

Analysis of the separate fragments of the specimen revealed that in the normal eye the protein content of the final fragment of the specimen regularly exceeded that of the first fragment In another context (*Krause & Raunio* under preparation) it will be shown that in pathological conditions the sequence of events may be reversed Within the range of the aspiration rates used changes in rate did not appear to affect the steepness of protein increase Slow aspiration might maintain a nearly normal composition of the aqueous humo but when process is prolonged the chance of error increases (effect of anaesthesia mechanical irritations etc) In practice it is difficult to extend th period of aspiration beyond 6–7 min On the other hand a too rapid and complete evacuation of the anterior chamber means that the aqueous humou of the posterior chamber is mixed with the specimen and also the permeability system may undergo a sudden change This type of situation was not studied in the present series

Only the very first part of the specimen may indisputably be considered pure primary aqueous humour as it exists at the tip of the needle at the moment of puncture This is true at least as long as the protein content of the aqueous humour is studied while it does not necessarily apply to its other ions and compounds

The aqueous humour of the three oldest patients of the series contained more proteins than the specimens of the young subjects *François Rabaey & Frans* (1958) believed to have found that individuals of advanced age normally have a higher protein content than the young ones

Summary

The potential sources of error associated with the paracentesis of the anterior chamber are discussed and a new paracentesis gun is presented A method is described by means of which a specimen is collected in a narrow plastic tube and fragments of the specimen are separated by air bubbles The rate of

aspiration is mechanically adjustable The mean protein content of normal aqueous is 11 2 mg % As the volume of the specimen increases the protein content of the aqueous humour increases Only the first fragment of the specimen represents normal aqueous humour The advantages and contraindications of the method are discussed

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CORNEAL OPACITY IN FAMILIAL PLASMA CHOLESTEROL ESTER DEFICIENCY

BY

EGIL GJONE and BJÖRN BERGAUST

Introduction

Familial plasma cholesterol ester deficiency (plasma lecithin cholesterol acyl transferase deficiency) has recently been reported in three adult sisters as a new clinical syndrome (5 6 10 11) The characteristic clinical features (Gjone and Norum (5)) were corneal opacity proteinuria normochrome anemia and a turbid or milky plasma which appearently was deficient in α lipoprotein and had very low levels of cholesterol esters Total cholesterol phospholipids and triglycerides were elevated in plasma of the two eldest sisters and the concentration of lysolecithin below normal in all Bone marrow and kidney glomeruli contained foam cells Abscence of plasma lecithin cholesterol acyltransferase (LCAT) was demonstrated as the fundamental defect in this inborn error of metabolism (Norum and Gjone (10)) The erythrocytes had a target cell appearance and contained increased amounts of cholesterol and lecithin (Gjone Torsvik and Norum (6))

In this article a more detailed description of the corneal changes in these three sisters is given We believe that the corneal opacity is a characteristic feature of this new syndrome

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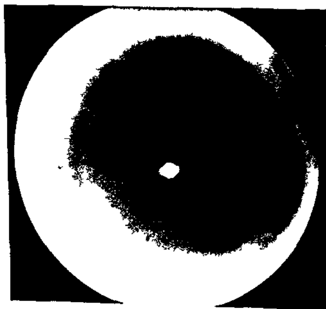
The three sisters 21 32 and 34 years of age had all the same kind of corneal opacity presumably from early childhood There was a slight difference in the amount of corneal opacity in the individuals the cornea being most clouded in the 32 year old sister Vision had always been good and none of them has had any ocular com plaints

On clinical examination the eyes were pale Cornea showed a nebulous cloudiness and near limbus a pronounced opacity of annular shape resembling an arcus lipoides senilis (Fig 1) Slit lamp examination revealed a regular and brilliant corneal surface The corneal curvature and the thickness of stroma were normal The corneal opacity was localized to the parenchyma and was composed of innumerable minute greyish dots (Fig 2) According to the distribution of dots the cornea may be divided in 1) a pupillary zone 2) an intermediate zone and 3) a peripherical zone (Fig 3)

1) In the pupillary zone these dots were abundant and evenly distributed in all layers of the stroma

2) In the intermediate zone the dots were less numerous in the anterior part of the stroma whereas the posterior part was full of dots

3) In the peripherical zone the number of dots in the anterior part of the stroma was increasing in limbal direction and a dense band was formed referred to as arcus lipoides (Fig 4) The arcus was separated from limbus by a narrow relatively clear zone of corneal tissue The border line at the outer edge of the arcus was irregularely



Fi 1
Annular opacity

From The University Hospital Rikshospitalet Oslo Norway
Medical Department A (Head Professor Paul A Owren M D)
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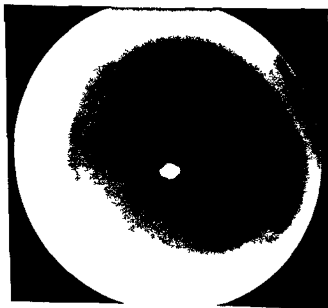


Fig 1
Annular opacity



Fig 2
Slit lamp photography Minute greyish dots in pupillary and intermediary zone



Fig 3
Sketch Pattern of opacity in corneal stroma

split and blurred because of a great variation in the number of stromal dots Close to the limbus all stromal dots vanished The appearance of the descemet membrane and the endothelium seemed normal as did the remaining parts of the eye The visual acuity in all eyes was 5/5

Discussion

According to Feldman (3) the average total lipid content of cornea is 1.24% of the corneal wet weight Corneal tissue is rich in neutral lipids representing



Fig 4
Slit lamp photography Dense band in the peripherical zone

34 1 % of the total lipids Little knowledge has been presented concerning the transport of lipids in cornea but accumulation of cholesterol and cholesterol esters particularly the latter is generally believed to be the cause of the opacity in arcus lipoides senilis (Andrews (2))

The enzyme defect in our patients may lead to generalized changes with accumulation of cholesterol in a variety of cells and membranes and it may be reasonable to believe that also their corneal opacity may represent lipid deposits The youngest of the three sisters had normal amounts of total cholesterol phospholipids and triglycerides and still she had a distinct corneal opacity The deposits are therefore not related to the absolute amounts of plasma cholesterol but probably depend either on the LCAT deficiency (and the *ratio* free/esterified cholesterol) or on the abnormal plasma lipoprotein pattern

Opacities scattered in the corneal parenchyma are also seen in several other diseases Arcus lipoides senilis is the condition of corneal infiltration with lipid material most commonly encountered The annular opacity of our patients however was not sharply limited on its outer edge

In different types of primary hyperlipoproteinemias arcus lipoides may make its appearance as early as in the third or fourth decade of life (1) It is suggested that the development of arcus is genetically determined rather than a reflection of a generalized lipid disturbance (9)

In gargoylism there is more uniform cloudiness of the parenchyma composed of more distinct dots The stromal opacities are bigger and should not be mistaken in the parenchymatous heredo familial corneal degeneration of dominant type (Groenouw I) nor of the recessive type (Groenouw II) *In the* crystalline degeneration of Schnyder in which the plasma cholesterol may be elevated the opacity is more distinct and localized to the anterior part of stroma in the central area only The central cloudy dystrophy of Francois is

2-5

occupying the pupillary area and is found more dense in the deeper layers of the stroma Combinations of these two centrally localized types of corneal opacities with arcus lipoides senilis might probably resemble the findings in our patients at the first glance In the cystein metabolic disorder the nebulous cloudiness is regularly distributed over the entire cornea without the zone pattern of our patients In cornea farinata the fine dust like opacities are only in the posterior part of the stroma In Tangier disease (Familial high density lipoprotein deficiency) the cornea may be normal (8) or may show random soft densities in the entire corneal stroma presumably due to deposition of cholesterol esters (7)

Drugs such as chlorpromazine and chloroquine may cause caracteristic opacity in the corneal stroma Our patients however had never used drugs

It has to be concluded that corneal opacity as reported in our patients has not been described in any other disease These corneal changes may probably be regarded as a characteristic feature of this clinical syndrome and be of importance for its diagnosis

Acknowledgement

Financial support from Anders Jahres Fond is gratefully acknowledged

Summary

Corneal opacity is reported as a characteristic feature in the plasma cholesterol ester deficiency syndrome together with proteinuria anemia and turbid or milky plasma Three sisters with the disease have been examined Their corneae showed a nebulous cloudiness and an annular shaped pronounced opacity near limbus The opacity was localized in the parenchyma and was composed of innumerable minute greyish dots They were seen evenly distributed in all layers of the stroma of the pupillary area The annular opacity resembled arcus lipoides senilis but the peripherical border was not so sharply demarcated It is believed that the corneal opacity is due to lipid deposits as a consequence of abnormal plasma lipid and lipoprotein composition

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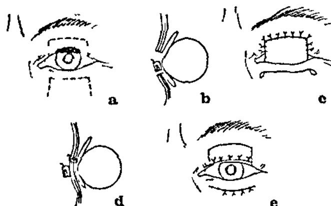


Fig 1

The principle of the Cutler Beard bridge flap operation *a* shows the excision and the flap outlined *b* shows side projection of the defect and the bridge. In *c* and *d* the flap is inserted into the defect carried behind the bridge of lower lid margin *e* shows the final result after cutting the pedicle

Case History

The patient is a 70 years old carpenter with a recurrent basal cell carcinoma of the upper lid margin. It started 2 years before surgery as a small ulcer and he received treatment at the local radiotherapy department where two courses of irradiation (5000 r / 90 kv and 5000 / 50 kv) was given at 11 month interval As the lesion grew despite of the radiotheraphy he was eventually referred to us for surgical treatment He then presented a basal cell carcinoma of the middle third of the right upper eye lid margin measuring 10 × 6 mm and creeping over the conjunctival limbus A biopsy confirmed the diagnosis

At the first stage of the operation a full thickness resection was done in a distance of 7–8 mm from the tumour A full thickness pedicle flap was raised from the opposing part of the lower lid leaving a 3 mm broad bridge of lid margin intact The flap was stretched behind the bridge and inserted in the defect. The subconjunctival tissue was united by buried 5–0 catgut sutures and so were the tarsal plate from the flap and the levator muscle The skin was closed by 6–0 interrupted silk sutures. The cut edge of the bridge was left raw covered by a piece of Jelonet, which also separated the conjunctica of the bridge from the skin of the flap A soft bandage was applied for ? days Stitches were removed on 6th day and the patient discharged for a fortnight – After an interval of 3 weeks the pedicle was separated at a second operation. Care was taken to cut the skin at the level of the lid margin but the conjunctiva 2 mm more distally to supply cover for the new lid margin and place the scar out of contact with the cornea The lower margin of the bridge was freshened and sutured to the lower cut edge of the pedicle

Only 3 weeks after the last operation the movements of both eyelids were normal and the closure complete The patient has since then had no complaints and he has kept free of recurrence for 2 years (fig ?)

From Radiumstationen in Århus and the Plastic Surgery Service under the Departments of Surgery Kommunehospitalet Århus

RECONSTRUCTION OF THE UPPER EYELID AD MODUM CUTLER AND BEARD

BY

N C PETERSEN

The reconstruction following full thickness loss of a larger part of the upper lid is generally considered a difficult problem Most of the methods available have got serious drawbacks and are not able to supply a movable upper lid with perfect corneal protection good esthetic quality and only acceptable sequelae at the donor area The bridge flap procedure described by *Cutler & Beard* (1955) and advocated by *Byron Smith* (1959 1966) seems to offer a good solution of the problem in most cases It shall be described and illustrated by a case

The principle of the operation

In the Cutler Beard operation the defect of the upper lid is substituted by a full thickness pedicle flap of lower lid placed vertically opposing the defect and leaving the lower lid margin intact At the first operation the flap is drawn behind the bridge formed by the lid margin and sutured to the margins of the defect The flap is then left to stretch for 2 month after which interval it is cut at a suitable level The pedicle slides back and is sutured to the distal surface of the bridge Cilia grafting can be carried out at the end of the interval or after the second operation but is generally omitted (fig 1)

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Fig 2
A basal cell carcin ma f the upper lid (A) is excise I an I the lefect replaced by a bridge flap (B) C an I D sh ws the final result

B



all – we preferred to cut the pedicle after an interval of 3 weeks instead of 2 month This makes the procedure even more acceptable and it might be suggested that the long interval is only indicated in cases with a particularly high defect

Summary

The problem of reconstruction of larger defects of the upper eyelid is discussed and a case treated by the principle of Cutler & Beard is presented The bridge flap procedure is recommended for wider use

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Further methods are available for the closure of larger upper eyelid defects but they all have their shortcomings Some of them shall be briefly discussed

One might fill the defect partly by a composite graft from the normal upper eyelid As a defect of the donor eyelid of 25–30 % can be closed by direct suture, a wedge of this size can be removed from the non affected upper lid and inserted into the defect This method however jeopardizes the function of a normal eyelid and unless the size of the graft is minimal the risk of necrosis is substantial

A pedicle flap from the neighbourhood, lined by a free mucosa graft is another possibility but a satisfactory result can not be anticipated The skin of the surrounding areas as forehead temple or zygoma has got nothing of the subtle quality of that of the eyelids Furthermore the lined flap is generally complicated by a severe degree of shrinkage of the lining

One might consider using a hinged flap from the lower lid The principle of this procedure has under the name of the Abbé flap, been used for many years when moving tissue from one lip to another Normally a defect of the upper lip is replaced by a wedge of lower lip tissue cut completely loose apart from a tiny pedicle at one side of the prolabium just large enough to contain the labial vessels The flap is rotated 180° around the small pedicle as a sagittally placed hinge The application of this principle for upper lid reconstruction is introduced by *Hueston* (1961) and advocated by *Mustardé* (1966) Obviously this extreme rotation is not favoured by the anatomy of the eyelids as of that of the lips and one might fear distorsion during the procedure Another drawback is the secondary defect of the lower lid which needs reconstruction by a pedicle flap sometimes even by a lined flap unless it is very small

The advancement of a tarso conjunctival flap from the opposing eyelid covered by a free skin graft was originally introduced by *Hughes* (1937) for repair of lower lid defects but has been used reversely This two layer cover can not compete with a full thickness transplant

The Cutler Beard operation seems to have none of the disadvantages mentioned above *Cutler & Beard* (1955) originally reported 12 cases and *Byron Smith* (1966) has added another two covering a variety of colobomas of the upper lid congenital or caused by fresh trauma scar tissue or removal of malignant tumours As in the case reported here the bridge flap has generally supplied a well functioning upper lid with a minimum of irregularity of the lid margin and caused no deformity of the donor site

In our case the operation was modified in some respects Not to mention the suturing which is less essential we did not find it justified to close the defect left on the distal surface of the bridge after the first operation and – first of

occur In fact the reaction did not occur continuously along the artery but at irregular intervals because a certain ratio is necessary between the two reacting substances before precipitation can take place In the vicinity of the reaction spot there is a total consumption of antigens and a new reaction does not take place till further on along the artery when the substances are present again in the required proportional concentration

Below a case of p r s is reported in a 52 year old woman (record no 150511/67) who was admitted to the Eye Clinic at Arhus kommunehospital from 3 8 67 to 19 8 67

In essentials the patient had previously been well During admission to a medical department in January 1966 a myxodema of the Hashimoto type was demonstrated with antibody formation against her own thyroid hormone The patient was discharged with tabl thyreodine Gea 100 units daily which she has taken since apart from a short period when the dose was temporarily increased to 200 units daily

In mid May 1967 the patient first noted eye symptoms in form of photopsia described as sparkling dancing particles first in the right eye and later in the left The patient saw an ophthalmologist who found vitreous opacities and arteritis and the patient was treated with tabl delcortin 10 mg × 3

After few days treatment the subjective troubles vanished simultaneously with

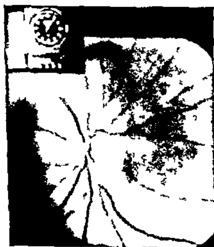


Fig 1
Ih t of retina SC
Several cuffs on a branch
of a nas sup dex



Fig 2
Fluorescent angiography 20 3 68
The cuffs on the previously affected branch have disappeared
and the contrast fluid flows freely

From the Eye Clinic Århus kommunehospital
Head Viggo A Jensen

PERI ARTERITIS RETINALIS SEGMENTALIS

BY

J ANDERS RASK

The ophthalmoscopic picture of peri arteritis retinalis segmentalis (p r s) is characterized by white plaques arranged in segments encircling the arteries like a cuff and localized to one or more arterial branches The affection abates in a period of weeks or months

The disease was first described in 1933 by Kyrieleis (4) who reported a case which he thought was a local allergic reaction to the tubercle bacillus or its toxins

Muncaster & Allen (1939) (7) and *Lyster & Bosborough* (1955) (6) each published a case that originated in association with an intradermal tuberculin test

In 1952 Thompson (10) described a case of irido cyclitis with the same retinal changes and in 1959 Griffin & Bodian reported three cases of the same disease – however no tuberculin test had been made in these last four patients just as no signs of tuberculosis were demonstrated Therefore p r s was considered a local reaction caused by other agents than tuberculosis

Kyrieleis (5) tried to explain the charecteristic segmentary diffusion from knowledge of the general rules of antigen antibody reaction p r s is seen during or immediately after a more or less pronounced chorioditis and the antigen was thus supposed to diffuse from a choriodal focus into the surroundings which include the vitreous body and thus be extra circulatory When after some time the production of antibody had begun and these antibodies had started circulating in the blood the antibodies would meet the corresponding antigens from the vitreous body in the arterial wall and precipitation would

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Summary

7 previously described cases of Peri arteritis Retinalis Segmentalis are reported
1 case of p r s caused by tabl thyreoidine is described

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5 *Kyrieleis W* Deutsch Ophth gesellsch 1967 61 78 82
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abatement of the arterial changes and the delcortin therapy was gradually reduced, but before it ended the ophthalmological changes grew more marked again, and so the therapy was renewed with an initial dose of 30 mg delcortin daily and she was admitted to the Eye Clinic at Århus kommunehospital

On admission the following was found v o d < 1 0 v o s 1 0 –1 25 sf Biomicroscopic examination o u nat Ophth o u slight vitreous opacities the papillae were slightly hyperaemic but well delineated the arteries slightly calibre changing with multiple cuff shaped segmented white plaques – about twice the diametre of an artery long – of several of the bigger arterial branches both central and peripheral and most marked in the right side The veins were natural and there was no retinal oedema just as no chorioidal foci were seen Fluorescent angiography showed natural passage of the affected arteries All uveitic tests were negative No signs of TB were demonstrated Biopsies from skin muscle and the mediastinal gland showed natural conditions Sedimentation rate 10 mm/h and Hgb 14 5 %

The patient was treated with tabl prednisone 10 mg × 4 resulting in gradual abatement of the retinal changes and the patient was discharged with 10 mg prednisone daily

After being discharged the patient had two recurrences The disease recurred when the steroid dose was below 7 5 mg daily After the maintenance dose had been kept at 7 5 mg daily there has been no recurrence The latest examination on 20 5 68 showed that the arterial changes had almost completely vanished only one or two small cuffs remained Fluorescent angiography still showed entirely free flow through the affected arteries

Discussion

Since the first description of p r s which was regarded as a local allergic reaction towards the tubercle bacilli p r s has been described several times without the demonstration of this specific agent and thus p r s must be assumed to be due to a local allergic reaction to widely different antibodies

The case reported here seems to be an allergic reaction to thyreodine a substance which only once or twice before in Ophthalmology has been seen to cause neuritis optica (2) and never before p r s

It has not been possible through the anamnesis to find other agent in this case For a short period the patient s thyreodine was discontinued but she could not manage without it and so continuation was decided upon as the arterial affection had a fair prognosis and it seemed possible to maintain her free of recurrences on a permanent dose of 7 5 mg delcortin daily

The differential diagnosis peri arteritis nodosa (8) arteritis temporalis (9) and lupus erythematosus (1) can be excluded as these diseases are associated with poor general condition and here the arterial changes are permanent

examination of our cases this problem has been solved by means of magnifying lens attached to the head of the ophthalmoscope

For this purpose the electric ophthalmoscope (May type) with comparatively wide focal area has been selected and mounted with the magnifying *lens 12 ×* (*Modified product of Optical Industry Ljubljana*) *the distance* between the lens and ophthalmoscope amounting 10 mm (Fig 1) The light of ophthalmoscope having passed the magnifying lens has been thus concentrated in an area 4–6 mm in diameter It goes without saying that other types of ophthalmoscope may be also employed usefully Magnification has been strengthened or lessened by adding plus or minus lens of the Rekoss disk The image of chamber angle thus obtained has been excellent provided the saline solution has been clear Examination has been of course performed in the supine position of patient Nasal and temporal segment of the chamber angle has been viewed from the top head side the lower and upper segment from the temporal side of patient (Fig 2) the observer s eye and hand being changed according to the situation The examination has been *performed in the extreme version of the patient s* eye However the iris root recess of the angle as well as the posterior third



Fig 1
Electric ophthalmoscope mounted with magnifying lens 12 × used in the examination of chamber angle of submerged eye

From the Ophthalmic Clinic – Rebro in Zagreb (Jugoslavia)

EMPLOYMENT OF THE OPHTHALMOSCOPE IN GONISCOPY OF SUBMERGEND EYE

BY

PETAR SOKOLIC M D

In examination of chamber angle by means of contact prism some pressure against the bulb is unavoidable This pressure may have some influence on the width of chamber angle In other cases it may appear harmful Method of examination which does not require any pressure against the bulb is gonioscopy by means of saline solution without the contact prism This method deserves accordingly to be taken into regard in cases wherein any pressure against the bulb is to be avoided

The simple technical equipment purposed for flooding the eye with saline solution has been described in our previous papers (Acta Ophth 45 1967 and 46 1968) and need not be described repeatedly It is visible from the figures presented in this paper that the same equipment is suitable for the employment of various viewing instruments coming into regard in the examination of chamber angle of the submerged eye In the above mentioned papers the technique of examination with detached head of microscop held in the hand and stabile binocular microscope as well as monocular ophthalmic loupe has been described In the present paper the examination of chamber angle of submerged eye with the ophthalmoscope is to be demonstrated

The essential advantage of ophthalmoscope is the incorporation of illuminant and viewing instrument In this respect ophthalmoscope appears very convenient for the examination of chamber angle of the submerged eye To our experience the simplest way to see the chamber angle of the submerged eye is to view the angle by means of ordinary electric ophthalmoscope provided with plus 20 D However magnification thus obtained is insufficient In

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the case of gonioscopycally closed angle to test whether the angle is closed organically or only gonioscopycally Goniosynechiae may be tested in the same way

In the cases with glaucoma simplex the free hand may try to provoke the blood in the Schlemm s channel by making homolateral or bilateral pressure on jugular veins in the fossa carotica This is most convenient to perform when the observer is viewing the lower segment of angle from the temporal side of patient As known the appearance of blood in the Schlemm s channel has differential diagnostic value in distinguishing between the trabecular and intrascleral glaucoma (Krasnow et al) Results of examination in this recept should be reported on another occasion

The examination of angle with ophthalmoscope in the manner described presents to our experience the most comfortable method of gonioscopy of submerged eye and the examination may be accordingly started by his method It may be sufficient for ordinary purpose of gonioscopy However in difficult cases necessitating a clearer stereoscopic image the examination may be proceeded with the stabile binocular microscope as it has been described in the above mentioned papers

Disadvantage of the examination of chamber angle by means of saline solution without contact prism is that examination of angle is performed in the version of eye so that cooperation of patient is necessary To our experience there is a category of patients wherein the examination is performed easily in contradistinction to that one wherein the bad cooperation may necessitate repeated examination

Summary

Technique of the employment of ophthalmoscope in the examination of chamber angle by means of saline solution without contact prism has been described

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Fig 2
Examination of the lower half of chamber angle of submerged eye with electric ophthalmoscope mounted with magnifying lens 12 ×

of trabeculum could be examined in a version of moderate degree well tolerated by the patient

Practically important advantage of the employment of ophthalmoscope in the examination of chamber angel is the ease of manipulation and the incorporation of the illuminant and viewing instrument as already mentioned The other advantage is that only one hand is occupied by the instrument the other hand remaining quite free for the performance of the manoeuvre which may come into regard

The free hand may perform the corneal pressure by means of glass rod in

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The occurence of the ERG invariably coincided with the occurence of the receptor outer segments (Differences in degree of development were found not only between different populations but also between animals within the same population Therefore it is essential that each animal that is studied with ERG is also studied with respect to its ultrastructure Otherwise no true correlations can be done) In no case was an ERG obtained prior to the development of the outer segments However an electrical response was found even when the receptor outer segments were very small and not identifiable in the light microscope At this stage although small the recepter cell showed all the morphological features of the adult cell except that the synaptic structures were completely lacking

The photopigment is known to be located in the receptor outer segment. Therefore it seems unlikely that a response to light stimulation should occur prior to the development of the outer segments On the other hand as soon as the formation of the outer segments has begun the receptor cell ought to be able to set up a potential upon light stimulation. This concept fits very well with the findings of the present investigation The ERG at this early stage consisted of a small purely negative wave which is most likely an isolated receptor potential

At somewhat later stages the outer segments were bigger At the same stage the negative potential was more pronounced Its duration was longer as well

At the age of 9 or sometimes 10 days the ERG of the *Rana pipiens* tadpoles suddenly showed a positive wave following an initial negative one This change in the electrical response always coincided with a morphological change the maturation of the synaptic structures at the receptor terminal This observation confirms the findings earlier reported for the *Rana catesbiana* tadpoles (although the change in the latter species came later due to a slower rate of development) The present investigation adds a new evidence in support of the idea that the a wave of the ERG represents the negative receptor potential and that the positive b wave is generated in more vitreally located neurons

(This investigation was supported by grants from the Swedish Medical Research Council projects no 14 X-734-01 K 67 14 X-734-0 A K 69-14 X-734-03 B by grants from H Hiertas Fund and by grants from the U S Public Health Service)

C Daunius *Routine applanation tonometry with Fluress®*

Applanation tonometry with Fluress® (Quickert Arch Ophth ,34 196,) was compared to applanation tonometry using separate solutions for anesthetic agent and fluorescein with respect to time With Fluress® a reduction of time with 25 % was achieved from around 140 seconds with separate solutions for anesthetic and fluorescein to 105-110 seconds Schiötz tonometry required the same time as applanation tonometry with *Fluress®* Schiötz tonometry in 137 eyes gave a false too low value of 3 mm Hg or more in 45 % *of the eyes* which is in good accordance with the results of an earlier study (Arch Ophth 50, 196)

The composition of Fluress® *is* well *suited* for routine applanation tonometry

I Anjou & O B Hannesson *A case of sarcoidosis with the picture of bilateral optic neuritis*

A new 5 year old painter had undergone ophthalmological examination in 196? and 1964 his visual acuity then being 1.0 *in both* eyes with a normal fundus bilaterally He had a history of well *regulated* diabetes mellitus since 1964 In January 1967 he on two occasions had intense pain over *the left* temporal region and in the left 1 of the forehead lasting *for 3-4 days* This was associated with burning pain over

TRANSACTIONS OF THE SWEDISH OPHTHALMOLOGICAL SOCIETY

EDITED BY

O Pallin Secretary

Meeting in Kalmar, March 23–24, 1968

B Rosengren & R Tornquist *Cooling of the sclera during diathermy coagulation for retinal detachment*

The advantage of cryo coagulation in retinal detachment surgery is that it leaves the sclera undamaged On the other hand nothing in principle suggests that cryo coagulation *per se* would be a better method than diathermy for producing retinopexy A weakness of the cryo method is that it is not associated with any visible scleral changes enabling the surgeon to estimate the depth of coagulation This must be done ophthalmoscopically Nor is it possible afterwards to recognize the treated scleral area

For a few years now I have consequently tried to modify the diathermy coagulation procedure in order to reduce the extent of the scleral lesions The method has now been further developed with the introduction of distilled ice water which is dropped directly on the sclera and thus acts as a coolant Diathermal coagulation then gives a patchy brownish slightly greenish discolouration of the sclera but no charring of its surface The charred surface layer that in diathermy coagulation sometimes is attached to the electrode and has to be wiped off is no problem when ice water cooling is used

The clinical trials conducted so far number merely 3 cases with 2 operations in one of those From these cases however it appears that an adequate choroidal reaction can be induced with significantly less scleral damage

Mirdza Germanis R Barkman G Karpe & Anna Stina Malmborg *Preservatives in eye drops*

To be published in Acta Ophth

E Palm & A Anseth *Transplantation of the parotid duct into the conjunctival sac in alacrimia with corneal xerosis*

S E Nilsson *The earliest detectable ERG during retinal development A correlation of structure and function* (From the Departments of Ophthalmology and Pathology Karolinska sjukhuset Stockholm and the Department of Zoology University of California Los Angeles)

The aim of the present study was to investigate further the morphological basis for the different components of the ERG Populations of very young tadpoles (*Rana pipiens*) were followed daily with ERG The earliest stage at which a light stimulation was followed by an electrical response was at the age of 6 days after fertilization Sometimes no answer was found until the age of 7 days One eye from each animal was used for ERG and the second eye was studied with electron microscopy

was characterized by deep central scotomas However in view of poor fixation and co operation they were difficult to determine in degrees

The visual acuity improved successively in the course of a month to R E. > 1 0 and L E. 0 4 and in the course of 2 months to R E 2 0 L E 0 7 After 2 months the colour sense was defective bilaterally The right visual fields were then normal but a 5–10 central scotoma persisted on the left side

Three and a half months after the previous acute loss of vision there was a recurrence with a decrease to P+L. It developed in the course of a few minutes while the patient was walking and was experienced as a haze

This time regression was more rapid After one week the visual acuity was R E 2 0 L F 0 6 In other respects the course was similar to that on the previous occasions with decreasing central scotoma and physiological fundi The right visual field was completely restored whereas a 10° central scotoma persisted on the left side The colour sense was normalized on the right side but not on the left.

Otoneurological examination disclosed slight spontaneous nystagmus to the left of central origin The general neurological state was normal Electrophoresis of the C S F showed changes of the same type as on the previous occasion although less pronounced The EEG was normal Roentgenological examination of the lungs revealed a slight increase in the paratracheal adenitis and mild definitely fresh parenchymal lesions of sarcoidosis type Psychiatric examination gave no grounds for suspecting a hysterical disposition The iritis was bilaterally unchanged in a quiescent stage

In this case the existence of sarcoidosis in a fully developed stage and with intracranial involvement can be regarded as established Although the clinical picture was most like that of acute optic neuritis the exceedingly acute and the completely simultaneous affection of both eyes distinguished it from the customary one Involvement of the optic nerves in the region of the optic chiasm would be compatible with the picture an in good agreement with several reports that intracranial sarcoidosis has a site of predilection in the pituitary infundibular region The sudden onset of the visual impairment indicates a mechanical process rather than a toxic one which has been stated by several authors to be the cause of optic nerve lesions in association with sarcoidosis One can perhaps envisage the existance of local arachnoiditis causing cystic encapsulation under pressure and on rupture of a shieldning wall a sudden pressure effect and possibly a toxic one as well on the neurons

B Johansson I Bartholdsson & K Mortensen *A case of orbital teratoma*

Anna Stina Friksson *Oculoglandular tularemia*

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O Pallin & P Algvere *Ultrasound examination combined with X ray examination as a diagnostic aid in a case of ocular proptosis*
To be published in Acta Ophthalmologica.

Meeting in Lund May 25–26 1968

A Anseth & E Palm *Corneal surgery at the University Eye Clinic Lund 19 5 196*

the same region when it was touched During these periods his left eyelid was stated to have hung down so that the eye was half closed In connexion with the first attack the visual acuity of his left eye decreased and remained approximately the same until the current examination

He was examined at the Eye Clinic in Jonkoping on Nov 8 1967 and then had bilateral iritis in the right eye there was only a medium fine aqueous flare whereas in the left eye fully developed iritis of plastic type was present with old firm posterior synechiae While awaiting hospitalization and investigation customary local treatment with atropine and topical administration of corticosteroids was instituted

Investigation on Nov 27–30 gave the following positive findings roentgenologically demonstrable hilar and paratracheal adenitis as in sarcoidosis slight eosinophilia and a slight increase in globulin chiefly in the gamma fraction on serum electrophoresis, but an E S R of only 6 mm/hour Since the patient was eager to resume work he was discharged from hospital Local therapy was continued

Five days later he was admitted as an emergency case a sudden pronounced loss of vision having occurred bilaterally 4 hours previously, when he lifted a sack weighing 15 kg He experienced the decrease in vision as a dark curtain coming from above the same on both sides Concurrently he had moderate pain over the forehead On examination the visual acuity of both eyes was P with completely exact I The discs showed nothing abnormal and no changes were present in the media or fundi which coulde explain the loss of vision The right pupil was wide and did not react to light which could be ascribed to the local atropine treatment The left pupil was bound with synechiae

His general neurological state was normal Serum electrophoresis disclosed the same slight changes as 2 weeks before but in the cerebrospinal fluid all protein fractions were raised to 2–3 times above the upper normal limit indicating increased vascular permeability Roentgenological examination showed that the lymph node enlargements had decreased but had not regressed completely The lung parenchyma was still unaffected Relatively fresh lymph node swelling must have been present previously since regression was distinct in the course of 10 days

Biopsy according to Daniels was performed In one specimen consisting mainly of adipose tissue occasional epitheloid cells but no giant cells were present in an orange sized lymph node Although this finding supported the diagnosis of sarcoidosis it did not constitute proof

Encephalography as well as right and left sided carotid angiography with special attention focused on vessels around the optic chiasm and third ventricle disclosed nothing abnormal

The Mantoux test was negative and the vitamin B_1 content of serum was normal

The diagnosis of sarcoidosis was thus based on the following observations bilateral iritis positive pulmonary findings negative Mantoux test results of biopsy examination as well as eosinophilia and slight changes in serum electrophoresis Definitely pathological changes in the protein content of the C S F indicated involvement of the central nervous system

The severe decrease in vision to P present on admission was combined with completely exact I indicating visual field remains relatively peripherally During the first week after the dramatic loss of vision successive improvement took place to finger counting at the site of the eye with concurrent increasingly distinct normalization of the outer limits according to Donders At the end of the week the outer limits perimetrically were normal on the right side but still slightly concentrically limited on the left side Thus with the still severe impairment of vision the clinical picture

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Three and a half months after the previous acute loss of vision, there was a recur rence with a decrease to P+L It developed in the course of a few minutes while the patient was walking and was experienced as a haze

This time regression was more rapid After one week the visual acuity was R E. 20 L E 0 6 In other respects the course was similar to that on the previous occasions with decreasing central scotoma and physiological fundi The right visual field was completely restored whereas a 10° central scotoma persisted on the left side The colour sense was normalized on the right side but not on the left.

Otoneurological examination disclosed slight spontaneous nystagmus to the left of central origin The general neurological state was normal Electrophoresis of the C S F showed changes of the same type as on the previous occasion although less pronounced The EEG was normal Roentgenological examination of the lungs revealed a slight increase in the paratracheal adenitis and mild definitely fresh parenchymal lesions of sarcoidosis type Psychiatric examination gave no grounds for suspecting a hysterical disposition The iritis was bilaterally unchanged in a quiescent stage

In this case the existence of sacroidosis in a fully developed stage and with intracranial involvement can be regarded as established Although the clinical picture was most like that of acute optic neuritis the exceedingly acute and the completely simultaneous affection of both eyes distinguished it from the customary one Involve ment of the optic nerves in the region of the optic chiasm would be compatible with the picture an in good agreement with several reports that intracranial sarcoidosis has a site of predilection in the pituitary infundibular region The sudden onset of the visual impairment indicates a mechanical process rather than a toxic one which has been sta ed by several authors to be the cause of optic nerve lesions in association with sarcoidosis One can perhaps envisage the existance of local arachnoiditis causing cystic encapsulation under pressure and on rupture of a shieldning wall a sudden pressure effect and possibly a toxic one as well on the neurons

B Johansson L Bartholdsson & K Mortensen *A case of orbital teratoma*

Anna-Stina Eriksson *Oculoglandular tularemia*

G Aurell *Some cases of eye muscle paralysis treated with operation and or th ptic training*

O Pallin & P Algvere *Ultrasound examination combined with X ray examination as a diagnostic aid in a case of ocular proptosis*
To be published in Acta Ophthalmologica

Meeting in Lund May 25–26 1968

A Anseth & E Palm *Corneal surgery at the University Eye Clinic Lund 19_8–196*

The increasing importance of keratoplasty during the last years is due to technical improvements new effective drugs against infections and other post operative reactions, and increasing understanding of the physiology and pathology of the cornea

Therapeutical keratoplasty in severe cases of keratitis as a supplement to the conservative treatment of these cases increases the importance of the lamellar technique in modern keratoplasty

The best results of keratoplasty are obtained if it becomes part of the routine work at the clinic and the surgical activity is kept at a certain level Thus one can expect improvement in the work and the personnel becomes familiar with this special branch of ophthalmology

During the 10 year period 1958–1967 252 keratoplasties were performed 133 penetrating and 119 lamellar

Keratoconus

Penetrating keratoplasty in 70 eyes The visual acuity (v a) increased in 66 was unchanged in 3 and decreased in 1 eye

These excellent results show that penetrating keratoplasty is a safe treatment of this corneal disorder

Keratitis

Penetrating keratoplasty in 38 eyes The v a increased in 27 was unchanged in 6 and decreased in 5 eyes

Lamellar keratoplasty in 68 eyes The v a increased in 43 was unchanged in 11 and decreased in 14 eyes

In healed cases of keratitis keratoplasty is performed for optical reasons The depth of the opacities in the corneal stroma determines the surgical technique to be used

In cases of active keratitis surgery is performed to stop the infection or to save the eye If possible the lamellar technique is used The optical results in these cases are usually bad

Dystrophies

Penetrating keratoplasty in 17 eyes The v a increased in 13 was unchanged in 1 and decreased in 3 eyes

Lamellar keratoplasty in 13 eyes The v a increased in 10 eyes was unchanged in 2 and decreased in 1 eye

Familiar dystrophies are usually well suited for keratoplasty either lamellar or penetrating depending on the depth of the corneal opacitites The visual results are usually satisfactory

Chemical and thermical burns

Penetrating keratoplasty in 7 eyes The v a increased in 3 was unchanged in [illegible] and decreased in 2 eyes

Lamellar keratoplasty in 17 eyes The v a increased in 7 was unchanged in 7 and decreased in 3 eyes

Chemical injuries with lime or lye have a very bad prognosis Repeated operations are necessary in most cases but the results are usually very depressing Radiation therapy of any kind seems to decrease the healing properties of the injured tissue and should not be used in these cases

H Bynke *The neuro ophthalmological unit at the University Eye Clinic Lund and its work 1956–1968*

B Linder *Cryo techniques in ophthalmology equipment and application*

O Holm *Basic problems in measurement of the pupillary aqueous flow* To be published in Acta ophth

O Wiebert *Effect of Diamox on the pupillary aqueous flow* To be published in Acta ophth

T Krakau *Photoelectric measurement of the pupillary aqueous flow*

A considerable simplification of the photogrammetric method for determination of the pupillary flow of aqueous (Holm Krakau 1966) is achieved by a photoelectric modification A wide beam of light from a slit lamp illuminates the pupillary area and the light from a volume of the anterior chamber in front of the pupil is measured by means of a photomultiplier

If the anterior chamber contains fluorescein the amount of the fluorescein in a small cuvette in the anterior chamber will be measured The cuvette contains a source of newly formed clear aqueous (= the pupil) If the content of the anterior chamber is well mixed the volume of inflowing clear aqueous must in the beginning be exactly the same as the volume of fluorescein solution lost over the boundaries on the cuvette If the photocurrent is recorded on a paper moving with constant velocity a linearly falling curve will be drawn The slope of this curve depends on the flow volume per time unit

The patient has to keep his eyes well fixed through 10–15 seconds when the recording takes place

G Stigmar *Dark adaptation studies in a case with steatorrhoea*

A 22 year old woman with steatorrhoea since early childhood and with multiple signs of long standing absorptive deficiency such as skeletal deformities and K hypovitaminosis was found to have an abnormal dark adaptation Her visual acuity was normal and there were no pathological changes in her retinae Subjectively she did not suffer night blindness She was treated with small doses of water soluble vitamin A and the improvement of the dark adaptation was easily reproducible after withdrawal and readministration of the vitamin After a single dose of 3000 IU the dark adaptation was normal but after half that dose adaptometric response was subnormal The amelioration of the adaptation threshold appeared quite obviously in 4 hours after the administration There was only a very slight improvement even after larger doses of fatsoluble vitamin A

The adaptation curves were recorded by means of an automatic adaptometer (Krakau Öhman 1966)

I Rendahl *Juvenile retinal detachment and ERG* To be published in Mod Probl Ophth

S F Nilsson *Electron microscopic demonstration of virus particles in human corneal epithelium in dendritic keratitis* (From the Departments of Ophthalmology and Pathology Karolinska sjukhuset Stockholm)

A 4 year old man, who was treated in 1961 for a keratitis of the left eye suffered a recurrence in 196 He had pains in his left eye for two days before be came to see the ophthalmologist On slit lamp examination several stained dendritic ulcers with an appearance typical of herpetic keratitis were seen on the corneal surface Under visual control in the slit lamp microscope a strip of the corneal epithelium was carefully removed The strip included one of the dendritic ulcers The remaining part of the strip three mill meters in length consisted of epithelium that appeared to be completely intact The tissue was immediately put in osmium tetroxide fixative and then

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more were considered pathologic A change of 9 milli osmol in the serum osmolality was marked as significant

The study confirms

1) The high percentage of the pressure peak 20–30 minutes after ingestion of water
2) The maximum fall in serum osmolality occured after 20 minutes from the ingestion of water
3) The necessity of determinations of haemodilution to evaluate the test.

G Stigmar *Relationship of Vernier and Stereo acuities*

Having many factors in common vernier and stereo acuities can be expected to be correlated It is also well documented that the threshold values of both kinds of acuity are of the same order of magnitude Most earlier investigations however are affected by the fact that different test methods have been used The automatic apparatus for time series analysis of visual acuity (Krakau 1964) seems to be the ideal instrument for a comparison since the vernier situation can readily be changed into a stereo scopic one with a simple prismatic device without altering other conditions

In the preliminary study reported the test object was arranged as a two peg test with different separation distances between the test details and varying time of exposures The test object were small enough to give only foveolar images and were viewed by the subjects from a distance of 5 meters The mean level of acuity during an eight minute period was calculated

The threshold values obtained are equivalent to values reported earlier (*about ? seconds of arc*) for a test object with an angular separation between the test details of about 5 minutes of arc and a total extension of 20 minutes of arc The time of exposure was 4 seconds

In the experiments it was found that the vernier acuity was more markedly reduced by increasing the separation distances than the stereo acuity The reversed effect could be recorded when the separation distances were decreased With fixed test objects and decreasing time of exposure there is also a possibility of separating the vernier and stereo acuities

A detailed report of these experiments will be published later

B Ehinger *Adrenergic retinal neurons*

Adrenergic retinal neurons have been demonstrated with the fluorescence micro scopical technique of Falck and Hillarp In mammals and birds there is always a layer of adrenergic fibres between the inner nuclear layer and the inner plexiform layer Another adrenergic fibre layer can occur in the middle of the inner plexiform layer and a third in the innermost part of the inner plexiform layer but these layers vary considerably between different species Variations can occur even between dif ferent monkey types Adrenergic perikarya occur most abundantly in the innermost cell row in the inner nuclear layer Adrenergic cells also occur in the ganglion cell layer and rarely in the inner plexiform layer None of the adrenergic cells send any process to the optic nerve

The fish retina displays an entirely different picture The layering in the inner plexiform layer is much less regular A dense adrenergic fibre layer is situated at the horizontal cells

Chemical analyses have shown that dopamine is the main transmitter substance in the retinal adrenergic neurons However microspectrofluorometric analyses have demonstrated that certain cells contain noradrenaline Morphologically these cells are indistinguishable from those containing dopamine

prepared for electron microscopy The necrotic cells of the dendritic ulcer contained a large number of virus particles morphologically identical with herpes simplex virus. The present investigation however mainly deals with cells taken from the intact part of the preparation and located about 2 millimeters away from the closest dendritic ulcer In electron microscopic survey pictures the cells appeared to be normal and without any signs of pathological changes At somewhat higher magnification however scattered intranuclear structures with an appearance typical of viruses were seen. Using serially cut sections it could be shown that every cell nucleus within the area investigated contained such particles The number of virus particles was fairly small compared to the virus content of the necrotic cells of the dendritic ulcer On the basis of the intranuclear localization and on the basis of comparisons with the structure of viruses isolated in experimental virology the particles could be identified as virus particles Each particle consisted of two parts the inner core and the outer capsid The core which is known to contain DNA appeared in the sections roughly spherical Osmium molecules were bound only to the peripheral parts of the core The diameter of the core was 450–500 Å The capsid which is protein in nature appeared in the sections as a roughly spherical shell with a diameter of 900–950 Å

The present investigation showed that in dendritic keratitis viruses may occur more generally in the corneal epithelium and not only in the visible lesions

H Bynke *Does tonometry and tonography influence the ocular blood flow?* To be published later in Acta ophth

K Dyster-Aas *Disturbance of the blood aqueous barrier in rabbits induced by endotoxins*

The term endotoxin is used to denote a toxic substance of a lipopolysaccharide nature localized in the cell walls of gram negative bacteria Injection of these substances into experimental animals provokes a great number of biological and toxic effects including fever leucopenia skin reactions shock and death In the eyes disturbances of the bloodaqueous barrier (indicated by an increased aqueous flare) transitory increase of intraocular pressure and hyperaemia have been observed Numerous gram negative bacteria are already present in the normal intestinal flora In certain conditions such as gastroenteritis peritonitis etc they appear to cause endotoxaemia with subsequent shock and damage to the kidneys

It has been suggested that uveitis may also be initiated by endotoxins Up to now there has been no generally applicable clinical diagnostic method for estimating the endotoxin activity A photo electric method for measurement of aqueous flare variations presented in a previous publication has been used to estimate the changes of aqueous flare in rabbits following intravenous injections of various endotoxins Doses of endotoxins as low as 0 25 microgram gave significant increases of aqueous flare with a characteristic time course The aqueous flare maximum is easily separated from the one found after injections of MSH and MSH activated serum Dose response curves have been constructed

J Cristiansson & O Mertens *Water drinking test combined with measurement of serum osmolality*

The water drinking test combined with measurement of serum osmolality has been used on 20 patients with suspected chronic simple glaucoma The intraocular pressure was measured by applanation tonometry every 10 minute after the ingestion of water and blood samples for determination of serum osmolality was taken every 15 minute during 60–90 minutes Patients with a rise of intraocular pressure of 6 mm Hg or

D i s c u s s i o n *H Skydsgard H Ehlers*

H Ehlers Recommended the proposal very earnestly

In many countries such societies had been founded a long time ago There was even an international committee of such national societies

The reason why we had so far hesitated was the fear of harming the existing societies of the blind and their care for those who are already blind To day however social care is so much improved that the time must have come for founding a Danish society for preventing blindness

Such a society should be open to everyone but the planning of the fight against diseases should of course be in the hands of medical experts

Recommended that those present gave the President the strongest possible support allowing him a free hand in the preparatory work which must necessarily take some time Finally wished the President luck in the project

V Dreyer was re elected member of the Committee of the Light Technical Society

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E G r e g e r s e n *Current Views on the Management of Strabismus*

During the past 10 15 years a number of different views have prevailed within the management of strabismus This applies to the treatment of amblyopia with eccentric fixation and to the orthoptic treatment of abnormal correspondence as well as to the question of the optimal indication for and time of operation. Opinions are still divided but the situation appears to be sufficiently clarified for an attempt at assessment.

Treatment of amblyopia with eccentric fixation

Amblyopia with eccentric fixation has been attracting much attention during the past decade The sensory physiological aspects have been studied and much time energy and ingenuity have been expended on the treatment As is well known the pioneers of this work are Bangerter and Cuppers who introduced pleopti treatment with their dazzle technique and after image technique etc However this complicated and time consuming treatment is on the decrease its range of indications getting ever more restricted

Pleoptic treatment of squint amblyopia with true eccentric fixation can as a rule considerably improve the vision if a permanent squint has not set in until after the age of 1½ ? years But although this treatment is primarily effective in many patients it is not indicated for children over approx 9 years or for adults with amblyopia and eccentric fixation since the therapeutic results generally will not keep in such cases if the vision in the other eye is good The fact is that generally bifoveal fusion or spontaneous alternation cannot be obtained in such patients so for this reason the therapeutic results will not be lasting

If the patients are over approx 9 years of age there is also a risk of doing them harm by pleoptic treatment which in that age group may produce permanent diplopia In children under about 6 years of age the complicated pleoptic methods are not prac ticable because of lacking cooperation Thus the complicated pleoptic methods of treat ing squint amblyopia with true eccentric fixation are indicated and applicable only in the age group approx 6-9 years and even in this age group pleoptic treatment does not always yield more than conventional occlusion therapy possibly supplemented by red filter technique or inverse occlusion.

The reason why conventional occlusion therapy may act upon amblyopia with ec centric fixation in children aged about 6 9 years and younger may be that there has

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BY

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The optimal situation for operation

The third aspect for ever topical concerns the optimal situation for operation i e the optimal time and optimal indications These two factors depend largely upon what is believed to be gained by an operation This may be illustrated by 2 different examples representing two extremes

The first example is that of a child with a squint who had never had normal binocular function or who has well developed abnormal correspondence with abnormal fusion when first seen, i e either a child with a permanent congenital squint or a child with a long lasting acquired permanent squint which has arisen in early childhood As is apparent from what has been stated above bifoveal visual function can hardly be obtained in such a case As a rule one must rest content if the operation results in so called microstrabismus*) i e a residual squint of about 5° or less Patients with microstrabismus usually have or get well developed and useful harmonious abnormal correspondence If in addition it is possible to make the child alternate spontaneously and keep a vision of 6/6 in both eyes the situation must be considered satisfactory from the functional as well as cosmetic point of view

Gradually it has become widely accepted that microstrabismus and a harmonious abnormal correspondence which is most commonly the result of treatment in patients with permanent congenital strabismus or with a well developed abnormal correspondence is preferable to the persistent struggle to obtain bifoveal visual function. Microstrabismus is no cosmetic handicap and harmonious abnormal correspondence in a patient who alternates is not an unfavourable situation, as already mentioned The alternative is the continuous struggle to obtain bifoveal visual function which requires a re operation each time there is merely a slight residual permanent and manifest squint postoperatively In between the operations alternating occlusion has to be practised and after the age of 5 years also orthopic treatment in the objective angle This treatment is an economic strain and requires a great deal of time and in spite of all these efforts it often does not lead to the desired result viz bifoveal visual function if the patients have a congenital permanent squint or a well developed abnormal correspondence with abnormal fusion

It has not been generally substantiated that better results are obtained by operating on infants with congenital strabismus around the age of 6 12 months than e.g at the age of 2 3 years In the case of children with a large congenital esotropia with a restricted abduction ability in the eyes an operation about 1 year of age is often advantageous In other cases of congenital strabismus it is often more reasonable to defer the operation until it is possible to obtain an impression of the position of the eyes in all parts of the gaze field and of the visual acuity in the right and left eye. Thus an operation for congenital strabismus is often best deferred until the age of 2 (or 3) years If congenital strabismus is operated upon as late as about 6 years of age the children cannot be expected to obtain so useful and well developed an abnormal correspondence as if they had had the operation earlier

If the squint angle is only about or less than 5 10° and the situation is absolutely acceptable from the cosmetic point of view there is no reason for operation if the patient has well developed abnormal correspondence and abnormal fusion. On the contrary it may be said that after the operation the patient can no longer utilize his useful abnormal correspondence

*) Microstrabismus or microtropia is here taken to mean any tropia of approx. 5° or less with abnormal correspondence.

been a question of false eccentric fixation. In children of this age it is seldom possib to differentiate between true and false eccentric fixation.

Thus the range of indications for the complicated pleoptic methods of treatment has now been considerably narrowed and it is possible that in the future this method of treatment will be used predominantly for patients with amblyopia and true eccentric fixation who have lost the vision in the good eye.

Let it be emphasized that the failure of the pleoptic methods of treatment to comply with the expectations makes early consistent, conventional occlusion treatment and prophylaxis of the amblyopia all the more important.

Orthoptic treatment of abnormal correspondence

The other aspect which has been reconsidered is orthoptic treatment of abnormal correspondence. During the past two or three decades great efforts have been made in many places to correct the abnormal correspondence by orthoptic exercises.

According to experience however it has been found that in squinters who have at the commencement of the treatment a fixed abnormal correspondence with abnormal fusion it is rather seldom possible to establish normal bifoveal correspondence despite repeated operations and orthoptic treatment. This applies quite particularly to patients with small squint angles of about 10° or less as the foveal suppression in the squinting eye is the greater the smaller the squint angle.

Thus if a squinter when first seen, shows a fixed abnormal correspondence with abnormal fusion, there will be little chance of obtaining normal bifoveal binocularity. This is a fairly common therapeutic situation occurring in most cases of congenital permanent strabismus with a small squint angle (i e 5 10° and less) and in similar cases acquired early but referred late for treatment.

Well developed abnormal correspondence has proved resistant to orthoptic treatment. Therefore instead of trying to obliterate the well developed abnormal correspondence by administering orthoptic treatment in the objective angle it is sometimes and in some places felt advantageous to improve the abnormal correspondence by administering the orthoptic treatment in the subjective angle. In that way the abnormal fusion may be extended and possibly an abnormal stereopsis and abnormal convergence may be developed and trained. Improvement of the abnormal retinal correspondence is of course only indicated when the cosmetic situation is acceptable i e the deviation is less than 5 10°. However it must be emphasized that often it is hardly worth trying to improve the abnormal retinal correspondence by orthoptic exercises as daily life affords better training than orthoptic exercises.

Summing up it may be said that orthoptic treatment with the object of obliterating a well developed abnormal correspondence with abnormal fusion is not in general indicated and in most cases not possible. True orthoptic treatment may be carried out in order to improve an abnormal correspondence but in many cases it is doubtful whether this orthoptic treatment improves it more than do the activities of daily life.

On the other hand orthoptic treatment is definitely indicated for the treatment of unstable normal retinal correspondence or of *incipient* abnormal retinal correspondence as may be observed in intermittent strabismus or in children who have been squinting for only a short time. In such cases orthoptic treatment can usually consolidate or establish a solid normal correspondence with satisfactory fusion range. Preoperative consolidation of an *unstable normal retinal correspondence* increases the chances of obtaining a bifoveal visual function after the operation. Postoperative consolidation of an unstable normal retinal correspondence is also indicated and rewarding provided that the position of the eyes permits a bifoveal visual function.

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According to experience however it has been found that in squinters who have at *the commencement of the treatment a fixed* abnormal correspondence *with abnormal* fusion it is rather seldom possible to establish normal bifoveal correspondence despite repeated operations and orthoptic treatment This applies quite particularly to patients with small squint angles of about 10° or less as the foveal suppression in the squinting eye is the greater the smaller the squint angle

Thus if a squinter *when first seen shows a fixed abnormal correspondence* with abnormal fusion there will be little chance of obtaining normal bifoveal binocularity This is a fairly common therapeutic situation occurring in most cases of congenital permanent strabismus with a small squint angle (i e 5 10° and less) and in similar cases acquired early but referred late for treatment

Well developed abnormal correspondence has proved resistant to orthoptic treatment Therefore instead of trying to obliterate the well developed abnormal correspondence by administering orthoptic treatment in the objective angle it is sometimes and in some places felt advantageous to improve the abnormal correspondence by administering the orthoptic treatment in the subjective angle In that way the abnormal fusion may be extended and possibly an abnormal stereopsis and abnormal convergence may be developed and trained Improvement of the abnormal retinal correspondence *is of* course only indicated when the cosmetic situation is acceptable i e the deviation is less than 5 10° However it must be emphasized that often it is hardly worth trying to improve the abnormal retinal correspondence by orthoptic exercises as daily life affords better training than orthoptic exercises

Summing up it may be said that orthoptic treatment with the object of obliterating a well developed abnormal correspondence with abnormal fusion is not in general indicated and in most cases not possible True orthoptic treatment may be carried out in order to improve an abnormal correspondence but in many cases it is doubtful whether this orthoptic treatment improves it more than do the activities of daily life

On the other hand orthoptic treatment is definitely indicated for the treatment of unstable normal retinal correspondence or of *incipient* abnormal retinal correspondence as may be observed in intermittent strabismus or in children who have been squinting for only a short time In such cases orthoptic treatment can usually consolidate or establish a solid normal correspondence with satisfactory fusion range Preoperative consolidation of an unstable normal retinal correspondence increases the chances of obtaining a bifoveal visual *function after the operation* Postoperative consolidation of an unstable normal retinal correspondence is also indicated and rewarding provided that the position of the eyes permits a bifoveal visual function

K Nørskov *Primary Glaucoma as a Cause of Blindness* Publ Acta Ophthal 46 (1968) 853 859

Discussion *H Skydsgard B Rosengren E Westerlund*

A Øther *Choroideremia and Xg Blood Group*

In a family with choroideremia a linkage analysis based upon Xg blood grouping showed that the genes for choroideremia and for the Xg blood group must be assumed to be situated far from each other on the X chromosome

J A Rask *Fat Emboli of a Retinal Localization*

Discussion *S E Simonsen P Brændstrup N Vedel Jensen Anna Frandsen*

412th Meeting 3rd November 1967 at the Eye Department Rigshospitalet Blegdamsvej

I Falbe Hansen *Experience of Diagnostic Ultrasound Examination*

Discussion *V Ehlers Viggo A Jensen S E Simonsen S Ry Andersen P Brændstrup*

K Nørskov *Clinically Diagnosed Primary Glaucoma on the Isle of Falster in 1960 Prevalence and Course* Publ Acta Ophthal 46 (1968) 853 859

Discussion *Viggo A Jensen*

J Edmund and H H Seedorff *Retinal Detachment Surgery III Surgery on the Retina* Publ Acta Ophthal 46 (1968) 666-673

H W Larsen and J Edmund *Indications and Applicability of Photocoagulation*

On the basis of the literature and of their own experience the authors reviewed the most important diseases of the fundus and anterior segment of the eye for which photocoagulation may be indicated The therapeutic results were illustrated by retinal photos etc

The most important fundal lesions which may be treated with advantage by photocoagulation are Retinal angiomatosis including Coats disease and telangiectasis of the retinal vessels Eales disease and proliferative diabetic retinopathy Lastly photocoagulation may be of value in the treatment of retinoblastoma but generally combined with radiotherapy and photocoagulation may be suited in special cases of retinal detachment

As a guidance in the photocoagulation treatment of proliferative diabetic retinopathy fluorescein angiography is used

To correct the pupil in the case of a drawn up pupil or the like photocoagulation therapy is superior to any other treatment

Choroidal nevi and conjunctival melanoma as well as choroid metastases are not suited for photocoagulation therapy

Discussion *P Brændstrup H H Seedorff S Ry Andersen J Edmund*

This was what may be said of the time and indication for operation in a squinter who has never had normal binocularity or who has a well developed and fixed abnormal retinal correspondence when first seen meaning in most cases a patient with congenital permanent strabismus or a long lasting permanent squint acquired relatively early The situation is quite different in a squinter in whom normal bifoveal function is preserved to a major or minor extent Squinters with preserved normal or subnormal bifoveal function have in most cases squinted for only a short time or else they have an intermittent or periodical squint or a squint acquired late In such cases operation should very often be done without delay also in cases where the squint angle is but a few degrees because it is very likely that in such patients normal bifoveal visual function will be achieved by operation possibly supplemented by pre and postoperative orthoptic treatment

Discussion *P Brændstrup V Dreyer N Vedel Jensen H Skydsgård G Poulher S Ry Andersen*

J Edmund and H H Seedorff *Retinal Detachment Surgery II Surgery on the Sclera* Publ Acta Ophthal *46* (1968) 643 665

Discussion *P Brændstrup B Rosengren H H Seedorff S Ry Andersen*

P Brændstrup Analysis of our material of retinal detachment in the Copenhagen City Hospital from the last 5 year period permits a follow up period ranging from 6 months to 5 years

Under the circumstances it was not relevant to aim at a prospective analysis of an extremely differentiated technique The method was changed when it was felt that a previously used technique ought to be replaced by a thorougly tested new procedure Most attention was given to simple interventions The main procedures which have succeeded each other were diathermy operation by the method of Larsson Weve scleral folding obtained by sutures and by the Custodis implant method During the past few years the majority of the cases have had operation by the Custodis method a smaller group by the cerclage method

During this period we have had a total of 123 cases with 156 operations and an attachment rate of [illegible]1 % The best results were obtained by the Custodis method which when considered alone gave an attachment rate of [illegible] %

B Rosengren Cryocoagulation has afforded a method which makes it possible to produce the needed exudative process in the choroid without damaging the sclera or other ocular structures Although the method may probably still be improved in several respects the advantages of this less traumatizing method have already manifested themselves As the effect of the folding procedures depends upon whether a folding is obtained which accurately involves the rupture and which is sufficiently deep the motivation for intrascleral procedures now seems in doubt These methods possessed the advantage that they left an outer undamaged layer of the sclera which makes later reoperation possible Since this motivation is no longer of the same importance attention must now be directed at folding operations upon the sclera in its entirety which fulfill the above demands

In cases where attachment cannot be obtained by conventional surgery injection of silicone into the vitreous is a possibility I do not think that one should aim at filling the greater part of the vitreous body but be content like Dr Seedorff with partial filling if this improves the visual function

ment it should be emphasized that by photocoagulation one may risk producing a gigantic tear along the coagulated area This complication has been reported in quite a number of cases and this is an important reason why Nordmann and Rosengren among others are very reserved in the matter of prophylactic photocoagulation unless quite special factors apply

Moreover it has been pointed out by Schepens that the cords which may occur on a level with the tear after photocoagulation constitute a serious complication He inclines to preferring an implant instead of photocoagulating such a tear One wonders whether cryocoagulation does not yield more in the treatment of tears without detachment – and at the same time complications are avoided

In our opinion at least prophylactic photocoagulations should only be used with the utmost reserve

S Ry Andersen Advised against photocoagulation of conjunctival naevi

J Edmund A tear situated on an implant may be finished by photocoagulation If the tear is localized at the edge of the implant or central to the edge, photocoagulation is too dangerous

N Ehlers and D Risse *Corneal Thickness and Intraocular Tension in Retinal Detachment*

The dependence of corneal thickness upon intraocular tension was studied in 45 patients with unilateral retinal detachment The results have been published in Acta Ophthal 45 (1967) 809

Analysis of the results of detachment surgery showed as is apparent from the figure that the prognosis was considerably poorer for eyes having a low tension than for normotensive ones

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Discussion *Mette Warburg I Falbe Hansen S Ry Andersen N Ehlers*

Extraordinary Meeting 1st December 1967
at the Eye Department Rigshospitalet Blegdamsvej

N Draganová Prague On Gel *Contact Lenses (Spofa Lenses)*

Discussion *E Gregersen O A Jensen S Ry Andersen H Skydsgard M S Norn*

413th Meeting 9th December 1967
at the Eye Department Rigshospitalet Blegdamsvej

BJERRUM LECTURE

Professor *Isaac C Michaelson* Jerusalem Israel *Epidemiological Aspects of Some Retinal Diseases* (Publ Acta Ophthal)
Ophthalmology in Africa (Publ Acta Ophthal)

P Brændstrup Let me take this opportunity to report our experience of the Zeiss photocoagulator in the Eye Department of the Copenhagen City Hospital I refer to the review I gave of photocoagulation its principle and range of indications printed in the report of our *Nyborg meeting in 1963 The indications have remained the same* plus a new range viz diabetic retinopathy for which the inspiration came from U S A

We have succeeded in sealing tears without retinal detachment as safely as has been described In several cases the tears have been so peripheral that they could not quite be reached by the coagulator so that they had to be treated by scleral diathermy

It may be difficult to decide on prophylactic coagulation of peripheral retinal degenerations in order to prevent detachment in cases where no tear is as yet present This has been considered only as a procedure on the latter eye when the other has been *treated for retinal* detachment *In 1963* I anticipated considerable activity *in this field* However we are still without clear and generally accepted instructions the attitude being still reserved In a small number of cases this treatment has been carried out without damage while in others the idea has been abandoned although we had broached the subject with the patients The explanation is of course that the therapist cannot radiate the optimistic *conviction inspired by clear indications*

Such a finishing touch has been tried in a few cases some time after operation for retinal detachment when the retina has become practically attached In one of these cases the result was poor The retina had been clinging very nicely to the implant impression but the edges of the tear were elevated The end result was total detachment and several small holes appeared around the original larger tear no doubt caused by the coagulations

Retinal periphlebitis with bleeding into the vitreous has been coagulated in only one case These are *rare cases in our Clinic which is a strange phenomenon* as Meyer Schwickerath found the condition to be common and a favourable object for treatment If done in time coagulation of the fundal periphery may arrest the process and preserve the important central areas

Conjunctival naevi have not been treated by us In such cases we act on the advice of our ophthalmic pathologists in the matter of surgical excision

In closing I should like to mention a case which we consider something of a triumph The patient was a three year old boy with bilateral retinoblastoma One eye was re*moved with a large tumour In the other eye there was a small* peripheral tumour treated without clinical cure in the Radium Centre I am entirely convinced that we succeeded in necrotizing this tumour by the photocoagulator Several sessions were needed In spite of its peripheral situation the tumour could be *grasped by a squint* hook after the eye had been softened by digital massage The condition has remained satisfactory during a five year follow up period The boy has had numerous ophthalmoscopies under general anaesthesia He developed a radiation cataract which was operated upon and radiation injury to the eyelid and cornea but to day his visual *acuity is 6/12 He has maybe the best function of* all known surviving cases of bilateral retinoblastoma in this country It is as if this one case has afforded the entire justification for the coagulator

In the future I could imagine that diabetic *retinopathy would afford an* indication for several photocoagulations and in my opinion it is important that we should use the same indications Other indications remain unchanged Patients with recognized retinal tears without detachment might be imagined to be referred more *often now* that we know Linder s thesis on the acute major collapse of the vitreous body in which he found tears in 15 % .

H H Seedorff In connection with the prophylactic treatment of tears without detach

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Extraordinary Meeting 1st December 1967
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N Draganová Prague *On Gel Contact Lenses (Spofa Lenses)*

Discussion *E Gregersen O A Jensen S Ry Andersen H Skydsgård M S Norn*

418th Meeting 9th December 1967
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BJERRUM LECTURE

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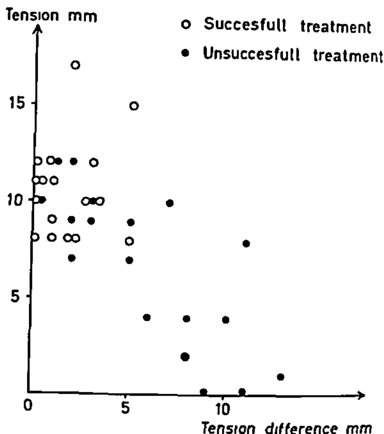
N Draganová Prague *On Gel Contact Lenses (Spofa Lenses)*

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413th Meeting 9th December 1967
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BJERRUM LECTURE

Professor *Isaac C Michaelson* Jerusalem Israel *Epidemiological Aspects of Some Retinal Diseases* (Publ Acta Ophthal)
Ophthalmology in Africa (Publ Acta Ophthal.)



N Ehlers and D Riise Detachment surgery

414th Meeting 2nd February 1968
at the Eye Department Rigshospitalet, Blegdamsvej

Communication from the President relating to the appointment of a commission for preventing blindness

D i s c u s s i o n *H Ehlers V Clemmesen H Skydsgard S Ry Andersen*

H Skydsgård Eva Rinziunski and M S Norn *Ophthalmologic and Orthoptic Examinations of Wordblind (Dyslectic) Persons* Publ Acta Ophthal 1969

D i s c u s s i o n *V Clemmesen B Lauæt V Dreyer S A Tordrup*

V Dreyer How can a distinction be made between primary and secondary dyslexia?

Did all 117 subjects have Gerstmann s syndrome or parts of this syndrome?

How can it be demonstrated that a retarded reading ability is not distributed according to a Gaussian curve and the selected subjects merely variants?

Answer The primary dyslectics of this material were selected according to the strictest psychological and paedagogical criteria not accepted as dyslectic or transferred to a school for dyslectics until they had been followed for one year during specia reading instruction at normal school

In general the dyslectics had only an incomplete Gerstmann syndrome

Boberg Ans a survey of 114 corneal grafts i e 102 penetrating grafts (P) and 12 lamellar grafts (L)

			Graft diameter (mm)								
A	No of eyes	pt	rcop	5 cl	5 not	5½ cl	5½ not	6 cl	6 not	6½ cl	6½ not
Keratocon	?2	16	4	1							
Seq to kerat	26	25	3	2		1	1	6	2	3	
Hp dendr ker	8	8	2	1				1		2	
Bull kerat	5	5	2	1				1	1	1	
Corn degen.	7	6	1					1			1
Syphil kerat	6	4	1			3		2	1	1	
Norm cornea (blind eye)	1	1							1		
foreign body	1	1				1					
Pterygion	1	1						1			
Total	77	67	13	5		5	1	12	5	7	1
B											
Burn	11	10	6					2	4	1	1
Neuroparal kerat	1	1	2		1			1			
Symp ophthal	3	2							2		
Microphthal	1	1							1		
Total	16	14	8		1			3	7	1	1

Among the selected subjects there was a strong family history of dyslexia (in 73 % of the series) and a characteristic sex ratio (male preponderance 4 1)

In a similar material published previously is was demonstrated *that the dyslexia is life long (S A Tordrup* Ph D school psychologist)

J Edmund *Experience of Corneal Grafting* (Publ Ugesk. for Læger 1969)

Discussion *H Ehlers J Boberg Ans P Barfoed G Larsen H Skydsgård K Dreisler E Westerlund O Thorkilgård S Ry Andersen*

H Ehlers Emphasized the stipulations of the new transplantation act.

J Boberg Ans Demonstrated his own results *of 114* grafting procedures which are apparent from the above table The *results were illustrated* by a large number of pictures

P Barfoed It is a pity that we are not going to *discuss the technique of* grafting to night The fact is that the more you work on these *operations* the more do the techni

Boberg Ans a survey of 114 corneal grafts i e 102 penetrating grafts (P) and 1? lamellar grafts (L)

Graft diameter (mm) Abbr cl clear not not clear

7		7½		8		8½		9		10		11		Total			
cl	not	cl	not	cl	not	cl	not	cl	not	cl	not	cl	not	clear P	clear L	not cl P	not cl L
2		9	2	1		6				1	1	1	1	2?		4	
2	1	1		7	1	1	1							22	1	6	
		3	1	1			1							3	5	1	1
		1		1	1									5		1	1
3				3										5	2	1	
														6		1	
																1	
															1		
															1		
7	1	14	3	13	2	7	2							63	10	15	?
1		2	6											6		11	
							1							1		?	
					1											3	
																1	
1		2	6		1		1							7		1/	
														70	10	3?	?

cal *problems get into the foreground* while the fear of autoimmune reactions wanes

The reason why the operation microscope is indispensable is that it is needed for placing the sutures so accurately that they do not get too deep whereby they injure the endothelium In that case local oedema arises If the injury is very small healing takes place but if this does not occur within 3 5 days the oedema persists and may even spread

The operation microscope is also indispensable in finishing the trepanation of the eye As the trephane penetrates aqueous fluid trickles out the trephane has to be re moved and the release of the blurred cornea must be completed by scissors This can not be done accurately except by the aid of the microscope

Regrettably the operation microscopes are not designed primarily for ophthalmolo gical use and therefore have to be modified They must magnify 10 times the distance from the objective to the patient s eye must be about 15 cm and the microscope should be able to swing sideways

Mette Warburg *Investigation of Refractive Media and Fundus in Patients with Nystagmus Demonstration of an Eyeball Fixer*

A contact lens of transparent plastic is provided with a handle The corneal part of the lens is cut out while its haptic part is intact After placing this lens on the eye it is possible by a light pressure backwards to immobilize the eye even in patients with coarse nystagmus and the eye may be rotated for removal of foreign bodies and treatment of keratitis The immobilizing contact lens is used for studying the eye in the slit lamp It comes in three sizes with a corneal hole of 10 11 and 12 mm Thus it is applicable for normal sized as well as microphthalmic and hydrophthalmic eyes The lens is manufactured by Friangs Optik Copenhagen

Discussion *H Ehlers V Clemmesen*

P Kjer and O Esbjerg Jorgensen *Ophthalmodynamometry in Carotid Occlusions and Stenoses*

First an historical survey on the development of ophthalmodynamometry since the method was described by Baillart in 1917

Thereafter the authors reported the results of examining 4? patients admitted to the Gentofte Hospital Copenhagen with evidence of infarction (37 patients) or transitory ischaemic attacks in the area supplied by the internal carotid artery (5 patients)

All these patients had a neurological examination as well as one or more arteriographies of the common carotid artery on one or both sides and more than half the cases also had central arteriography by the method of Seldinger The angiographies gave the following findings Carotid stenosis in 15 cases carotid occlusion in 6 occlusion of the middle cerebral artery in 4 atherosclerosis in 8 and normal appearances in 9 Moreover ophthalmodynamometry and ultrasonic pulse detection on the carotid artery were carried out in nearly all cases

The object of the study was to correlate ophthalmodynamometry and ultrasonic pulse detection on the carotid artery with the angiographic findings and to draw attention to the value of ophthalmodynamometry in patients with carotid occlusions and stenoses A pressure difference of 25 % or over between the two eyes was taken to be a positive ophthalmodynamometric finding

The investigations showed that the ophthalmodynamometry was positive in all cases of occlusion in the internal carotid artery while it was positive in only about half the cases with stenosis (presumably the most severe ones)

Ultrasonic pulse detection of the carotid artery revealed reduced pulsation in the internal carotid artery in all cases of occlusion and in many of stenosis but also in several cases of other arteriographic groups

The ocular signs – transient monocular blindness occlusion of the retinal artery with and without contralateral homonymous hemianopsia transient or permanent homonymous hemianopsia unilateral retinopathy miosis and diplopia – were related to the other angiographic findings

Six patients had vascular surgery In two of the operated patients a preoperatively positive ophthalmodynamometry had become negative with almost equal pressure on both sides In the third patient the result of ophthalmodynamometry was not quite significant before the operation there being only a 20 % difference between the two sides After the operation the pressure was the same on both sides In the fourth case ophthalmodynamometry was impracticable because of glaucoma and a history of embolus in the central retinal artery In the fifth operated patient ophthalmodynamometry had been negative prior to the operation In the last operated patient who had had a positive preoperative ophthalmodynamometry it proved impossible to restore the

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7		7½		8		8½		9		10		11		Total			
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														P	L	P	L
2		9	2	1		6				1	1	1	1	22		4	
2	1	1		7	1	1	1							2?	1	6	
		3	1	1			1							3	5	1	1
		1		1	1									5		1	1
3				3										5	?	1	
														6		1	
																1	
															1		
															1		
7	1	14	3	13	2	7	2							63	10	15	2
1		2	6											6		11	
							1							1		?	
					1											3	
																1	
1		2	6		1		1							7		17	
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marked in the hypophysectomized than in the control group Impairment of visual acuity and restriction of the visual field have been more pronounced in the control group Phlebopathy and haemorrhages decreased appreciably after the operation but slight recurrences have appeared in a few years All the patients were suffering from advanced proliferative diabetic retinopathy Progression of the proliferations was more pronounced in the control group and this also applies to progression of rubeosis iridis

Intraocular tension was low (average 12 mm Hg) in both groups Haemorrhagic glaucoma has occurred in 5 eyes of the control group but in none of the hypophysectomized group Changes in renal cardiac and neurological signs were very slight in both groups

This study is a team work being carried out by *K Lundbæk R Malmros H C Andersen J H Rasmussen F Bruntse P H Madsen and V A Jensen* A report was submitted to the 6th International Diabetes Federation Congress in Stockholm 1967 The study is being continued

Discussion *O A Jensen H W Larsen V A Jensen S E Simonsen H Skydsgård F Speets S Ry Andersen*

P M Madsen (in reply to H W Larsen) The visual acuity was expressed partly in the ordinary way by stating the acuity in Snellen s values before and after the operation However it is difficult to arrive at a mean value by this means Calculation of the mean of effective vision – visual efficiency – as advocated by A C Snell and S Sterling in Trans Am Ophth Soc 23 (1925) 204 227 gives a single value which is comparable in the various groups

This has shown between the first examination and the examination in January 1968 an impairment of visual efficiency of 8% for the operated patients but of 25% for the controls

Strict criteria were fixed for admitting patients to this project. The material comprises exclusively young patients with retinopathy threatening their vision but without renal or cardiac involvement The assignment of patients to the control group or the hypophysectomy group was entirely random Indeed the two groups have proved almost identical Rubeosis iridis was somewhat more common in the control than in the operated group but in return the first examination showed a larger number of cases with mild proliferative retinopathy in the control group Rubeosis iridis was often very mild consisting merely of a few small vessels at the pupillary margin.

S F Simonsen and D Riise *Cutting of the Optic Nerve and Intraocular tension* (Publ Acta Ophthal)

Discussion *P M Møller S Ry Andersen*

416th Meeting 30th March 1968
at the Eye Department Rigshospitalet Blegdamsvej

F Goldschmidt and M Nielsen *Genetic Guidance in Retinoblastoma* (Publ Acta Ophthal 46 (1968) 736 41)

Discussion *H Skydsgård S Ry Andersen*

passage through the internal carotid artery at the operation because of too extensive an occlusion

It was concluded that ophthalmodynamometry does not render arteriography superfluous but that it is suited as the first examination in obscure cerebral insults amaurosis fugax unilateral retinopathy, and the like

Furthermore a positive ophthalmodynamometry with a negative conventional common carotid arteriography affords an indication for the more comprehensive central arteriography in cases felt to be suited for surgery Considering the increasing number of cerebrovascular insults and the increasing therapeutic activity ophthalmodynamometry may in essential respects contribute towards the diagnosis of these diseases and to the postoperative follow up of the effect of a possible operation

Discussion *S Jensen B Lawætz P M Møller K Bech H Ehlers*
S Jensen referred to a study on oculosphygmography published in Acta Ophthal 46 (1968) 674 684

N Ehlers *A Case of Horizontal Micropsia* (Publ Acta Ophthal 46 (1968) 45 48)

Discussion *B Lawætz V Dreyer O Thorkilgard K Dreisler*

A Other *Experience of Contact Lenses for Aphakic Patients* (Publ Ugesk f Læger 130 (1968) 366 367)

Discussion *E Westerlund V Dreyer G Larsen*

A Other was admitted as a member of the Society

415th Meeting 9th March 1968
at the Eye Department Rigshospitalet Blegdamsvej

General Meeting

C Edmund in the chair
President s and treasurer s reports

Mette Warburg was elected member of the committee of the Danish Ophthalmological Society instead of *O A Jensen* who retired by rotation The committee then consists of *S Ry Andersen (President) M S Norn and Mette Warburg*

A draft suggesting the appointment of a commission for the prevention of blindness was thoroughly discussed The following members were elected for the commission *H Ehlers P Brændstrup V A Jensen P M Møller H Skydsgård and S Ry Andersen* As legal adviser *Jørgen Hansen* D C L was elected

The day of the Society meetings was discussed Friday or Saturday Several colleagues from the provincial towns are unable to attend on Fridays

P H Madsen *Hypophysectomy in Proliferative Diabetic Retinopathy*

A progress report on a controlled clinical trial of hypophysectomy for diabetic retinopathy was presented Two well matched groups of patients 15 totally hypophysectomized and 15 controls are being followed At present (after a follow up period of from 1 to 5 years) the ocular manifestations of diabetic retinopathy have been less

sympathetic ophthalmia But if applicable vision can be hoped for every effort should be made to preserve it even with a risk of sympathetic ophthalmia

Steroid therapy in manifest sympathetic ophthalmia does not afford a 100% guarantee of fully restored vision However the new potent steroids may be expected to afford a satisfactory result in the great majority of cases

Steroid medication may be either prophylactic or therapeutic The former means local steroid therapy early in the posttraumatic or postoperative course in order to alleviate an existing or expected prolonged reaction, as this is imagined to be able to prevent possible development of sympathetic ophthalmia However sympathetic ophthalmia has occurred in spite of such a prophylactic regime and a really reserved attitude to an early use of local steroids has been expressed In part, it may suppress the symptoms and signs which would otherwise herald incipient sympathetic ophthalmia and in part the treatment may inhibit the natural defence forces of the body Possibly the most correct attitude at present is to wait two weeks before administering steroids but I think most ophthalmologists display a more liberal attitude

Manifest sympathetic ophthalmia requires local and systemic steroids in large doses at least initially and one must be prepared for long lasting medication e g for a year

Sympathetic Ophthalmia

(1) Copenhagen City Hospital 1937 1967

15 patients 11 with senile cataract + 4 with perforations of the eyeball Five enucleations were done

	6 6	6 9 6/18	6 24 6/50	6/60
Pre steroid era	4	2	2	3
Post steroid era	3		1	

(2) State Institute for the Blind and Weaksighted

Children under 16 years of age

1900 1919	1920 1939	1940 1959	1960
17	11	5	0

The table lists the cases of sympathetic ophthalmia in the Eye Department of the Copenhagen City Hospital and in the State Institute for the Blind and Weaksighted through the past 30 and 68 years respectively The reduction in the number of cases after the advent of steroids is evident

J Edmund *The Eosinophil Cells in Perforating Eye Injuries* (Publ Acta Ophthal 46 (1968) 1175 1183)

Discussion regarding both papers *O A Jensen E Heidensleben H Skydsgård H Ehlers S Fog Andersen O Thorkilgård P Brandstrup J Edmund*

E Goldschmidt *Epibulbar Lipodermoids Preauricular Nodules and Polythelia in Three Generations*

S V Kessing *Epithelial Cysts in the Conjunctiva* (Publ Acta Ophthal)

Discussion *M S Norn K K Dresler S Ry Andersen*

M S Norn doubted whether the cysts were a sign of reduced production of mucus

S V Kessing stated that local reduction of mucus production e g on the upper tarsus may be the explanation of the conjunctival complaints

S V Kessing *Demonstration of the Collection of Macroscopic Eye Preparations of the University Eye Clinic*

Discussion *P Eldrup Jorgensen*

V Dreyer *On the Diagnosis of Colour Blindness with a Particular View to Occupational Ability* (Publ Acta Ophthal)

Discussion *Mette Warburg B Lawæt H Skydsgård K K Dresler H Ehlers Elise Vesterdal*

417th Meeting Weekend Meeting 4th and 5th May 1968 at Hotel Nyborg Strand Nyborg Subject Traumatic Ocular Lesions

P Brændstrup *Sympathetic Ophthalmia*

For more than a century our most important protection from sympathetic ophthalmia has been prophylactic enucleation

In order to attain its object the enucleation should preferably take place one week after a trauma or operation on the eyeball or at least not more than two weeks after In the absence of severe ocular mutilations the indication for enucleation must be based upon minor signs and this poses a clinical dilemma

The present generation of ophthalmologists has been trained in a liberal enucleation regime involving the sacrifice of an unknown but at least considerable number of sighted or potentially sighted eyes

During the past few decades there has been a distinct reduction in the number of cases of sympathetic ophthalmia and a number of our young colleagues have never seen one In my opinion this is due to (1) the ever increasing possibility of being treated by an ophthalmologist (2) the ever improving operative technique and (3) prophylactic enucleation which thus should not be given the main credit for this favourable development

Since sympathetic ophthalmia may be treated with steroids the time seems to have come for passing from a liberal to a stricter enucleation regime According to such a stricter regime an injured eye including an operated eye should be removed only if it is severely and hopelessly involved so that for this reason the patient is better rid of it Since this situation will usually manifest itself in the course of the first few post traumatic or postoperative days there is still room for prophylactic measures against

and steroids To day the incidence of the disease is hardly higher than what may be explained by a statistical coincidence of perforation and iridocyclitis due to other causes

The eosinophilic cells are extremely variable in their ways The count may be influenced by the action of light or by occlusion of the eyes

O Thorkilgård In the Eye Department of the Odense County and City Hospital we have for the past 3 years done daily eosinophil counts in all cases of perforating eye injuries starting on the 7th 10th day after the injury

During the period 1965 1968 we admitted a total of 101 patients with fresh traumatic perforation of the eye 24 of whom had intraocular foreign bodies

Only in two of these 101 cases do we recall that the result of the eosinophil counts influenced the choice of treatment These two ca es were briefly *reported* *An increase* in the eosinophil counts of from approx 300 eos/mm³ to 1500 eos/mm³ and 1000 eos/*mm³ respectively* occurred on the 16th 19th day and thereafter steroid therapy was instituted This treatment would hardly have been considered on the basis of the clinical course alone

Both cases were interpreted as phakoanaphylactic reactions

P Brændstrup The line of thought behind *Edmund's* studies is as follows (1) Sympathetic ophthalmia will possibly occur in particular *in patients whose systemic immune* reactions predispose them to this reaction unlike the average patient and (2) eosinophil counting appears to be applicable as *an indicator of this special* immune reaction pattern. In practice it may be used especially in the way that lacking *increase in the* eosinophil count speaks for preserving an injured eye

To this it may be objected that the eosinophil counts even when done quite *correctly* appear to vary in such a haphazard way that *there is reluctance* in attributing to them *any particular* value as a clinical criterion

If the formidable incidence of sympathetic *ophthalmia* from former times – *e g cl se on 50 %* in the Franco German War in 1870 – *are correct* it seems more likely that local ocular processes were operative *rather than* a systemic predisposition

Counting of eosinophil cells does not appear to be particularly relevant at present in deciding the indication for *enucleation which* in my opinion is more safely based upon purely ocular *criteria*

It w ul l be interesting to hear of eosinophil counts following operations on the eye p ssil ly also squint *operations* an l enucleation in general

W uld suggest that the few patients who have developed sympathetic ophthalmia shoul l be subjected *to extensive study* utilizing modern *immune* reaction tests in order thereby to ascertain a divergent reaction pattern rather than adhering to routine eosinophil counting *after eye injuries*

Possibly e sinophil counting *might* play a role in selecting the time of instituting steroid therapy

P Rasmussen and F Gjerris *Cranial Injuries – Neurosurgical Aspects*

Traumatic injury to the skull is a common event

Out of all fatal traumatic *injuries* (846 in Denmark in 1964) cerebral damage *is* responsible for one third Only a small proportion of the cranial injuries are admitted to neurosurgical departments Intracran al *haematomas* are believed to occur *in* 1 5 %

A material f 61* patients admitted during a *four year* period (1955 1958) to the Neurosurgical Department of the University *Hospital* Copenhagen was briefly re porte l Nearly all the injuries were severe There was a *surprisingly* large number of

O A Jensen I should like to discuss definitions in particular from the pathological point of view and to draw conclusions based mainly upon histopathological materials

When the injured eye shows a characteristic appearance which I shall describe in more detail in my first paper I prefer talking of sympathogenic ophthalmia of the eye an appearance known empirically to lead at times to a *sympathizing reaction* in the other uninjured eye if it reacts at all If it does and if the relevant clinical features are present we have what might be called *sympathizing ophthalmia* in this eye and *clinically* we have approached *sympathetic ophthalmia* as closely as possible as there are no clinical changes which permit a definite diagnosis If the second eye is enucleated too and exhibits the characteristic appearance we have histopathological *proof* of sympathetic ophthalmia

In my opinion

1 sympathogenic ophthalmia is rare
2 sympathetic ophthalmia even more rare – whatever may be the cause therapeutic or other – and this is a matter of great interest
3 sympathetic ophthalmia is decreasing in frequency – from numerous cases durin the American Civil War by way of about fifty during the First to no proven case during the Second World War
4 It is a reaction occurring mainly in young individuals and possibly also in persons with an autoimmune disease
5 In the presence of lenticular damage the likelihood of a phakoanaphylactic reaction is increased This may also manifest itself clinically as reaction in the other eye which is a commoner condition than sympathetic ophthalmia
6 If an apparently sympathetic state of the other eye occurs in an elderly patient especially in lenticular damage as during cataract extraction there is most likelihood of a phakoanaphylactic state

Clinically it may be impossible to distinguish the two states although certain lines may be laid down to go by

However it is very important to try to make a distinction as removal of lenticular material in the involved eye or eyes may bring the condition to a dramatic stop In this condition too the characteristic changes are most often encountered in one more rarely in both eyes

E Heidenslebcn In a material collected in the Eye Department of the Gentofte Hospital Copenhagen it was possible to demonstrate a significant increase in the average number of eosinophilic cells in a group of patients with perforating eye injuries In a corresponding group of patients with blunt non perforating eye traumas and in a group operated upon for cataract there was apparently also an increase in the eosinophil count but far from significant

On the basis of the fact that all patients with perforating eye injuries must be expected to show a definite increase in the eosinophil count it was stated that some reserve ought to be displayed in including fluctuations in the eosinophil count in the considerations when assessing a possibly threatened sympathetic ophthalmia

H Ehlers Occurrence of the same disease in paired organs is known also in other regions Sympathetic irritative reactions from one eye to the other are also well known but it is a far cry from here to assuming that sympathetic ophthalmia is present

At the beginning of this century sympathetic ophthalmia was a dreaded event But many of the cases were in fact entirely different diseases Histologically a number of the published cases from those times are reminiscent of tuberculosis and sympathetic ophthalmia decreased together with tuberculosis even before the advent of penicillin

and steroids To day the incidence of the disease is hardly higher than what may be explained by a statistical coincidence of perforation and iridocyclitis due to other causes

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Both cases were interpreted as phakoanaphylactic reactions

P Brændstrup The line of thought behind *Edmund*'s studies is as follows (1) Sympathetic ophthalmia will possibly occur in particular in patients whose systemic immune reactions predispose them to this reaction, unlike the average patient and (?) eosinophil counting appears to be applicable as an indicator of this special immune reaction pattern. In practice it may be used especially in the way that lacking *increase in the* eosinophil count speaks for preserving an injured eye

To this it may be objected that the eosinophil counts even when done quite correctly appear to vary in such a haphazard way that there is reluctance in attributing to them any particular value as a clinical criterion

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It would be interesting to hear of eosinophil *counts following* operations on the eye possibly also squint operations and enucleation in general)

Would suggest that the few patients who *have developed* sympathetic ophthalmia should be subjected to extensive study utilizing modern immune reaction tests in order thereby *to* ascertain a divergent reaction pattern rather than adhering to routine eosinophil counting *after eye injuries*

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P Rasmussen and F Gjerris *Cranial Injuries – Neurosurgical Aspects*

Traumatic injury to the skull is a common event

Out of all fatal traumatic injuries (346 in Denmark *in* 19(4) cerebral damage is responsible for one third Only a small proportion of the cranial injuries are admitted to neurosurgical departments *Intracranial* haematomas are believed to occur in 1 5%,

A material of 61% patients *admitted during* a four year period (1955 1958) to the Neurosurgical Department of the *University Hospital* Copenhagen, was briefly reported Nearly all the injuries were severe There was a surprisingly large number of

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Clinically it may be impossible to distinguish the two states although certain lines may be laid down to go by

However it is very important to try to make a distinction as removal of lenticular material in the involved eye or eyes may bring the condition to a dramatic stop In this condition too the characteristic changes are most often encountered in one more rarely in both eyes

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A material of 619 patients admitted during a four year period (1955 1958) to the Neurosurgical Department of the University Hospital Copenhagen, was briefly reported Nearly all the injuries were severe There was a surprisingly large number of

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choroid and vitreous body suggest numerous ruptures of veins and capillaries throughout the involved area. The most severe haemorrhages were found in the event of ruptured aneurysms on the anterior communicating artery In these cases (4 eyes) they were accompanied by vitreous haemorrhages haemorrhages around Haller s circle and in 3 of the cases by injury to the central vein where it passes through the dura 4 eyes from patients with ruptured aneurysm on the anterior or middle cerebral artery showed less massive haemorrhages In addition some propagation of blood from the subarachnoid space of the skull is likely to have occurred The following mechanism was suggested Initially the massive subarachnoid haemorrhage caused by the rupture of the aneurysm elicits arterial contraction in the involved area This causes anoxia and increased resistance whereupon the blood pressure and thus also the cerebral pressure undergo a violent but short lasting increase The initial increase in the blood pressure may elicit the haemorrhages and is rapidly followed by a fall of blood pressure and unconsciousness

Discussion *P Rasmussen V A Jensen*

P Rasmussen These studies of haemorrhages in the optic nerve and eyeball following subarachnoid haemorrhages are extremely interesting The haemorrhage and rupture of the aneurysm is accompanied by an increase in blood pressure often restricted to a few hours

The entire course of subarachnoid haemorrhage is obscure and it is incomprehensible why these patients fare so badly – 25 % die within the first 48 hours

We know that the minimal bleeding which as a rule occurs is in itself negligible The meningeal irritation gives rise to headache and a stiff neck and the secondary spasms are responsible for the neurological symptoms However neither can explain the fatal outcome or the frequently severe sequelae

The finding that bleeding may occur in the ocular fundus even in the vitreous body with no direct connection to the subarachnoid haemorrhage and that congestive phenomena may be observed in the vessels of the optic nerve implies that similar phenomena may be present in other parts of the brain – and in this connection the optic nerve must be interpreted as an outgrowth of the brain

Perhaps these observations may afford the impetus for further studies of the brain especially the hypothalamus following subarachnoid haemorrhage Interest should be centred on pressure circulatory problems and diapedetic bleeding

I Svane Knudsen *Traumatic Venous Thrombosis* (Publ Acta Ophthal)

Discussion *H Ehlers P Brændstrup B Lauritz*

H Ehlers The spontaneous venous thromboses are always discovered after sleep while arterial occlusions may occur during the day

V Nordentoft and Inge Lise Dalsgård *Retinal Haemorrhages in the New born*

Previous theories on the causes of retinal haemorrhages in newborn infants were reviewed

A series of 13 newborns were ophthalmoscoped through Richardson s contact lens at the latest 24 hours after birth with a particular view to the incidence of haemorrhages in infants delivered by vacuum extractor as compared with infants delivered spontaneously

There was no possibility of a comparison with infants delivered by forceps as this method has been almost completely abandoned at the Odense County and City Hospital

intracranial haematomas This is also taken to include the acute subdural accumulations which are not operable but indicate severe diffuse brain lesion Most of these haematomas were autopsy findings The total mortality was 31 % Among patients with dilated inactive pupils and affected respiration only one survived Half the patients with other brain stem symptoms survived Among patients with epidural haematomas the mortality was 24 % – partly due to severe associated brain damage and partly to the fact that in a few cases the haematoma was an autopsy finding

The mechanical and pathogenetic features of cranial trauma were summarized with particular attention on recent studies

When a skull sustains a trauma it receives an amount of energy which becomes absorbed in the cranial wall and in the cranial contents The skull exerts a dampening effect an effect which is increased when a fracture occurs At the site of the trauma a positive pressure is set up on the opposite side a negative pressure The equalization occurs in the reversed order

The most severe lesions often occur at the site of the contrecoup or cavitation

Apart from the pressure gradients the action of rotation is of great importance in brain injuries The most marked actions of rotation affect the border surfaces of the tissues

The most sensitive structure is the brain stem Even mild traumas *with short lasting* unconsciousness may cause instantaneous cessation of the function of the reticular formation

Right down to the cellular plane profound changes occur as a result of a cranial trauma It is assumed that the glial tissue is particularly affected and this involves severe metabolic disturbances The posttraumatic sequelae are most of all reminiscent of circulatory disturbances in the central nervous system

The great recent advances in the results of treating the traumas are not due particularly to neurosurgical efforts the injuries accessible to neurosurgery make up a negligible proportion The improved results must be attributed to better understanding of problems relating to fluid balance and nutrition more effective treatment of infections convulsions and hyperthermia better nursing care and improved anaesthesia

K Bech and F Gjerris *Serious Ocular Injuries in Cranial Traumas* (To be published)

Lis Mellemgård and F Gjerris *Traumatic Cortical Blindness* (Publ Acta Neurologica)

Discussion on the above three papers *P Brændstrup E Westerlund K Bech*

J A Fahmy and S Ry Andersen *Fundal Bleeding in Subarachnoid Haemorrhage Following Rupture of Intracranial Aneurysms*

A preliminary report was given on the relation between subarachnoid haemorrhages and fundal bleeding in a neurosurgical material of 160 patients admitted during a 3 year period to Neurosurgical Department S of the Århus City Hospital with a diagnosis of subarachnoid haemorrhage

S Ry Andersen and J A Fahmy *Ocular Histopathology in Subarachnoid Haemorrhage Following Rupture of Intracranial Aneurysms*

Report of the histopathological material so far comprising 8 eyes from 4 men who died in the Neurosurgical Department S Århus of ruptured intracranial aneurysm with subarachnoid haemorrhage

Disseminated multiple haemorrhages in the optic sheaths optic nerves retina

4 An elevated intraocular tension is *not* necessary This is important Previous authors have laid great stress upon the role of elevated tension We have definitely substantiated experimentally that pigmentation occurs almost as soon and gets just as intense at a normal as at an elevated tension, i e in a period of an hour or two Furthermore we have observed several clinical cases of corneal haemochromatosis un preceded by an elevated tension although in these cases it may of course be claimed that the tension may have been elevated during the interval between the measurements

5 Endothelial damage may be present The provision applies to *in vitro* experiments as it cannot be taken for granted that a tissue as sensitive as endothelium can always tolerate being removed from the body The histological sections might indicate that in our experiments there was always some endothelial damage *In vivo* such damage might easily arise by the pressure of the clot against the posterior surface of the cornea

6 The pigmentation is due primarily to haemoglobin This has been demonstrated by histochemical staining of corneal specimens from our experiments as well as from *enucleated eyes* with haemochromatosis In both events the histological appearances were exactly identical

7 The haemoglobin enters from the endothelial aspect and from the periphery This item has been the subject of much discussion Our *experiments appear to show that both routes* are possible Attempts at excising corneae with exclusion of the limbal vascular net nevertheless result in haemochromatosis On the other hand experiments on intact enucleated eyes have shown that the pigmentation is earliest and most marked in the periphery where it involves the stroma *through its entire thickness* indicating invasion by way of the limbal vascular net

8 Clearing is due partly to the breakdown of haemoglobin to bile *pigments partly* to histiocytic phagocytosis followed by intracellular *deposition of haemosiderin* The latter has been demonstrated by iron *staining of enucleated* eyes which had for a *long time* been the seat of corneal haemochromatosis

9 A special lamellar construction like that of the human cornea is necessary This is evident from the failure of ever inducing corneal *haemochromatosis* in rabbit eyes either in vitro or in vivo

10 Topical treatment by desferrioxamine has shown a favourable effect I shall *later revert to this item*

Let me show you the *appearance of* corneal haemochromatosis in a benzidine stained section. As you will see the stroma contains stainable deposits in between as well as within the lamallae *The distribution* through the stroma depends upon the duration of the haemochromatosis After the lapse of *some time* the specimens show the strange phenomenon that the staining is most marked beneath the epithelium This is because the basement membrane forms a sieve which does not permit passage of the haemo globin molecules during the flow *of* fluid from the posterior to the anterior *corneal* surface

As already mentioned the *presupposition of* corneal haemochromatosis is hyphaema regardless of its aetiology Since *however the great* majority of hyphaemas are of traumatic origin it is in *traumatology that* haemochromatosis is most often *encountered* In the slit lamp it *may be difficult* to discern incipient haemochromatosis on the back ground of the dark clot but it is of the *utmost* importance to detect the condition as the possibility of a good result depends upon early institution of treatment.

The treatment of hyphaema has *previously* been discussed int. al by *Gregersen* in this country and in Norway *Horven* has also published an *excellent* review

However something quite special applies *to corneal* haemochromatosis Every effort must be made to prevent further progression as *soon as the* condition has been *detected*

Haemorrhages were found in 40 % of the entire series and in 63 9 % of those delivered by vacuum extraction

The appearance of the haemorrhages was described particular attention being given to the cockade like haemorrhages It was pointed out that the haemorrhages were more severe in infants delivered by vacuum extractor The possibility of similar haemorrhages in the brain was suggested

An attempt had been made to analyse the material for the influence of various obstetrical factors upon the incidence of the haemorrhages but as yet it is too small The studies are being continued

Discussion *E Boisen H-W Larsen P Brændstrup*

E Boisen Submitted a case of traumatic retinal angiopathy (Purtscher) occurring after a fat embolus syndrome of traumatic origin

Owing to the changes in the blood values Purtscher s disease is assumed to be caused by the combined effect of vasomotor changes in the rheological status and a reduction in the colloid osmotic pressure as well as in the haemoglobin level

Hans Walter Larsen In connection with Dr *Nordentoft* s paper I should like to mention that in the University Hospital Copenhagen we have also performed a study on retinal haemorrhages in newborns presenting by the breech and in newborns delivered by vacuum extractor

Among 87 newborns we found 29 to have retinal haemorrhages i e 33 % which is in accordance with Nordentoft s findings

In addition we combined the study with neurological examination and EEG

This disclosed quite a good agreement between retinal haemorrhages neurological abnormalities and EEG changes

The most interesting finding however was that at follow up one year later we found only one patient a spastic to have a severely abnormal EEG and strabismus In another two the EEG was slightly abnormal but in these two patients and in all the others included in the follow up neurological findings and fundal appearances were normal

Therefore retinal haemorrhages neurological abnormalities and EEG changes during the first postnatal week may give some indication of the severity of the delivery but from these changes it is not permissible to draw any conclusions regarding the prognosis unless all the named studies have shown severe changes during the first week of life

Jens Falbe Hansen *Hyphaema and Corneal Haemochromatosis*

On a previous occasion and elsewhere – Dr *Edmund* and I have reported on the aetiology and pathogenesis of corneal haemochromatosis The report we submitted then was the result of an experimental study on excised human corneae as well as on enucleated human eyes The experimental results were compared with a number of clinical findings which have later been supplemented and confirmed Let me briefly sum up

1 Total hyphaema is not necessary In 2 cases a coagulated hyphaema was followed by corneal haemochromatosis corresponding precisely in extent to the clot

2 The formation of a clot is a presupposition In fact this follows from item 3 (haemolysis) as we know from Hørven s investigations that an unclotted hyphaema will be absorbed the red cells passing intact into the blood stream

3 Haemolysis is a presupposition Not until the red cells have haemolysed does haemoglobin get into contact with the cornea and not until then is there any possibility of a pigmentation

V A Jensen *Stereotechnique*

A film on the removal of foreign bodies from the eye by stereotechnique was shown The method will be published in Ugeskrift for Læger by *E Ratjen* and *V A Jensen*

Discussion *P Kjer V Dreyer S Ry Andersen*

O A Jensen *Ocular Traumatology Elucidated by a Danish Material of Enucleated Eyes* (Publ Acta Ophthal 46 (1968) 1194)

P Eldrup Jørgensen *Epithelialization of the Anterior Chamber A Clinical and Histopathological Study of a Danish Material* (Publ Acta Ophthal)

O A Jensen *Posttraumatic Recession of the Anterior Chamber Angle Clinical and Histological Findings* (Publ Acta Ophthal 46 (1968) 1207)

Discussion on the above three papers *V Clemmesen P Brændstrup S Ry Andersen H Skydsgård O A Jensen P Svane Knudsen K K Dreisler*

P Svane Knudsen Can anything be said about the prognosis of the phakoanaphylactic reaction in the sympathizing eye? Probably it is not as poor as for sympathetic ophthalmia? In the matter of treatment cortisone should be tried for as long as possible but for how long? A patient of ours still requires topical cortisone one year after a phakoanaphylactic reaction. Each time it is discontinued he has a recurrence.

In the case of traumatic cataracts in children I believe we all want to be conservative waiting for spontaneous maturation of the cataract so that merely one simple linear extraction is required It is still important I suppose to perform the fewest possible operations on the eyeball owing to the risk of phakoanaphylactic reaction.

K K Dreisler During the same period that phakoanaphylactic uveitis has been diagnosed with increasing frequency sympathetic ophthalmia has become a rare disease A number of the cases previously published as sympathetic ophthalmia have no doubt been erroneously diagnosed phakoanaphylactic reactions

Therefore it would seem reasonable to assume that *this is one and the same disease* On this assumption it might be worth trying to remove only the lens instead of the entire eye in a presumed case of sympathetic ophthalmia If this results in improvement as rapid as in phakoanaphylactic uveitis *the hypothesis would be supported* In practice it may of course be difficult to carry through intracapsular cataract extraction if the patient is young

M S Norn *Transparence of the Iris of Traumatic Origin Studied in the Slit Lamp by the Method of Abrams*

By transpupillary transillumination done by the method of *Abrams* it is possible to demonstrate in the pigment layer of the iris defects so small that they *must* represent the appearance of a single pigment cell

The investigation is carried out in a half darkened room The beam of *the slit lamp* should be of the same size or slightly smaller than the pupil The *patient* fixates the beam which is projected into the pupil while the visual axis of the eyepiece and the beam coincide The beam is projected obliquely in order to avoid a disturbing corneal reflex The slit lamp is focussed on the posterior surface *of the iris* corresponding to the anterior surface of the lens

In order to detect all the details *it is necessary* to adhere strictly to the rules of the method

As already mentioned the condition occurs in the presence of clotted hyphaema although fortunately only a minority of clotted hyphaemas give rise to haemochromatosis The treatment must consist in breaking down the clot if possible. To this end urokinase or thrombolysin may be used According to *Scheie et al* and *Horven* thrombolysin is entirely harmless in the concentration 1250 units/ml while *Horven* on the basis of rabbit experiments warned against urokinase However caution should be observed in concluding from rabbits to humans We have not seen toxic effects of this substance in clinical use On the other hand we have seen another untoward side effect in a single case to which I shall return

The technique is simple A limbal puncture is made with a neddle through which alternate cautious injection of the fluid and aspiration are done by moving the plunger to and fro As a rule it takes up to 10 minutes to break down the clot and thereafter the anterior chamber is rinsed with physiological saline According to *Scheie et al* however one case took up to 90 minutes before the clot had disappeared

The above mentioned unfortunate case of urokinase therapy was a case of clotted hyphaema of about one week s duration admitted to the University Hospital from Greenland There was no haemochromatosis This old hyphaema which was perhaps partly organized could not be dissolved the therapeutic efforts merely resulted in severe haemolysis In confirmation of the theories advanced above total corneal haemochromatosis was present on the next day but fortunately it subsided In such a case of an old clotted hyphaema it might perhaps have been better to be content with paracentesis in order to relieve the tension possibly combined with cautious irrigation with saline solution

Topical application of a 5% desferrioxamine ointment (Desferal) has proved encouraging Desferal forms with iron a chelate compound and although it cannot directly affect haemoglobin it is able to bind the iron which is released during the breakdown of haemoglobin As is well known iron is highly toxic to the tissues and it is therefore important to remove it Very probably a number of the permanent corneal opacities reported after haemochromatosis represent protein denaturation caused by iron All our haemochromatoses treated with Desferal cleared in a considerably shorter time than usually stated in the literature

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Hans Walter Larsen *Traumatic Fundal Lesions*

The fundal changes in non perforating ocular traumas (Berlin s oedema choroid rupture and haemorrhages) and in perforating ocular traumas (bite lesions and foreign body lesions) were described Lastly Purtscher s retinopathy and fundal changes in strangulation

The fundal changes were illustrated by 43 retinal photos

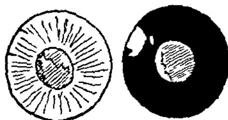


Fig 4

At the age of 10 years this patient sustained an ocular trauma by knocking two hammers against each other The ocular injury was not detected One year later he was found to have a traumatic cataract A shadow was demonstrable by X rays and the ERG was negative indicating siderosis

Transillumination showed a large peripheral defect and a more detailed slit lamp investigation revealed an appearance suggesting fine atrophy of the corresponding area of the anterior surface of the iris but so faint that it was not detected until the suspected area had been pointed out by transillumination.

It must be assumed that this defect was caused by the non diagnosed injury and that primary detection of this defect in the pigment layer of the iris would have occasioned a further primary examination of the eye

Several further examples of the applicability of the method in traumas were given

Conclusion

The transillumination examination is well suited for demonstrating defects in the pigment layer of the iris not only *immediately after the trauma* but also later when the demonstration may be of value in compensation cases Throughout life *the defect* will remain a proof of previous trauma

However the traumatic defects may be reminiscent of defects left by *acute glaucoma* or by iritis with a tendency to *synechiae* *On* the other hand they do not look like *the diffuse* motheaten transparence seen in *pigment glaucoma* heterochromic cataract sympathetic ophthalmia *advanced diabetes* or albinism or the sector shaped *motheaten* transparence which may be seen inferiorly in normal *subjects*

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Vorn M S Cataract extraction in Fuchs heterochromia Follow up of 19 cases Acta Ophthal 46 (1968) 685 699

H J Jensen Caterpillar Hair Injury to the Eye

Serous retinal detachment occurred in the right eye of a 56-year old male (case rec. 111,206) Forty nine years previously he had been *stung* in the eye by a caterpillar This had caused two weeks *later inflammation* which slowly subsided but left impaired vision and periodical moderate pain in the eye Slit lamp examination showed a corneal opacity at the site of entry *of the caterpillar hair or hairs* nodular structures *in the* underlying iris with synechiae to the *corneal* opacity and – after dilatation of the pupil – a caterpillar hair was seen *encapsulated* in the lens The theories of migration of *caterpillar hairs* in the human eye were briefly discussed

The figure on the left illustrates the anterior surface of the iris as seen in an ordinary slit lamp study while the one on the right is the result of transillumination

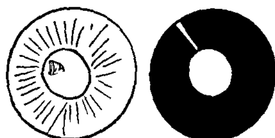


Fig 1

A 21 year old man was hit by a rotating steel brush Iron dust was found in the cornea in an intralamellar situation The condition did not appear to involve any danger and the patient was sent home Two days later he presented himself with a traumatic cataract and the chamber filled with fibrin Transillumination at the first visit would have disclosed a considerable radial defect in the iris pigment layer indicating that the injury was more severe than first assumed

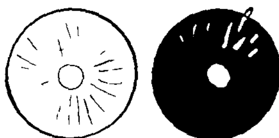


Fig 2

A 22 year old woman with anisocoria after a small hyphaema exhibited considerable defects in the pigment layer of the iris

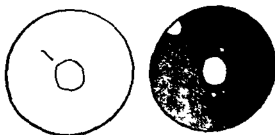


Fig 3

Thirty years previously a man now aged 41 had had a corneal perforation with a cilium in the chamber The pale cilium was just discernible on the anterior surface of the iris Transillumination disclosed dialysis of the pigment layer in continuation of the cilium

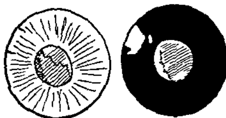


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H J Jensen *Caterpillar Hair Injury to the Eye*

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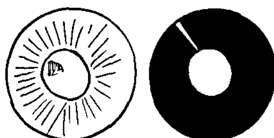


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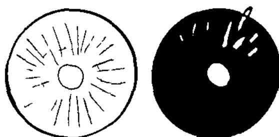


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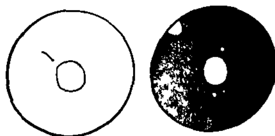


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recent tables It was emphasized that the current rates correspond as far as possible to the disability attendant on a given visual impairment as found in practice according to major statistical studies and are not based upon theoretical mathematical calculations as were the earlier rates

It will be noticed that the slope of the curves for disability percentages in bilateral visual impairment should be (and is) steep at visual acuities of less than 6/18 6/18 at which reading is impossible Visual acuities of 6/24 6/24 give 40 % disablement as compared with only 15 % previously 6/60 6/60 corresponding to the highest disablement pension is now assessed as 75 % previously 50 % Lastly a visual acuity of 2/60 and less on both sides corresponds to 100 % disability as such a small visual remnant cannot be assumed to be applicable for occupational purposes

Evaluation of the disability percentage for *restriction of the visual field has not been* fixed in tables in this country but we have a practice Most is awarded for bilateral defects the maximum for marked concentric narrowing so called tube vision there after in the order named for homonymous hemianopsia in particular right sided bi temporal hemianopsia and least is awarded for defects superiorly in the visual field In this respect the patient s occupation is of relatively great importance as the need for an orientating ability differs widely within the different occupations

Loss of the eyeball is only rated at 25 % (previously 30 %) i e the same rate as for a *phthisical eye* as it is estimated that the prosthetic technique is now so far advanced that the cosmetic result is just as good or perhaps even better than that if the injured eye remains

Rates for *diplopia* are 8 10 % as previously but these too are minimal rates In permanent palsy or dislocation of the eyeball requiring constant occlusion of one eye the rate may be raised to 20 % equal to the loss of *vision in one eye* depending upon occupation

Aphakia and anisometropia (e g in unilateral aphakia) *is not quite as* disabling as previously because of the possibility of using contact lenses but of *course regard must* be paid to whether the patient is able to wear the lens (*and insert it*) and to loss of accommodation 8 15 % compensation.

Cosmetic and other complaints e g photophobia *in changes* of the pupil pain, frequent instillations etc may raise the compensation by 5 10 %

Any increase in the rates owing to the victim s special abilities or special field of occupation is in the range 5 10 %

Thereafter the amounts in money were mentioned The compensations are fairly low but subject to changes according to the *cost of* living index under the workmen s c mpensation act higher under private *insurance* where the premium is higher too and highest in damages awarded in *court* The practical procedure in an accident insurance case was described In general the compensation in this country is paid as an annuity at disablement rates exceeding 50 % *as a lump sum at* lower degrees of disablement where the amount is intended rather to ease the period of getting accustomed to the disability

In this country the recommendation concerning the ocular disablement rate in accident insurance cases is written by an *insurance* doctor with no ophthalmological training but on the basis of an *ophthalmologist s statement* It is of the utmost importance therefore that these statements *give clear* and easily comprehensible data on the ocular condition at the t me of the *examination,* including the accurate visual acuity with and without correcting glass and whether *spectacles* can be used In addition the statement must include an accurate description *of other* kinds of ocular disablement and lastly an estimate of the prospects concerning future exacerbation or improve

A macrophoto of the encapsulated caterpillar hair was demonstrated (Publ Acta Ophthal)

Discussion on the two preceding papers *V Clemmesen O Thorkilgård S Ry Andersen H Ehlers*

H Ehlers Mentioned a patient who had been stung by a bee in the cornea The pigments of the eye disappeared but a few years later pigmentation had returned

J Edmund *The Prognosis of Perforating Eye Injuries* (Publ Acta Ophthal 46 (1968) 1165)

Discussion *S Ry Andersen*

Mette Warburg and H Skydsgård *Traumatic Blindness Experience Through 20 Years from the Institute for the Blind Copenhagen*

Elise Vesterdal *Accident Insurance Problems in Ocular Injuries*

The principles of assessing disability due to ocular injuries sustained in accidents were reviewed Since 1965 they have been coordinated in the five Scandinavian countries

The assessment is based partly upon "medical normal tables for assessing the disability percentage due to unilateral and bilateral visual impairment partly upon rules for evaluating other forms of ocular disability – not far removed from the proposals worked out in 1949 by the Danish Ophthalmological Society Commission for the revision of compensation calculations in eye injuries inspired to a marked extent by the studies of *Ruse* of Hamar Norway

It was emphasized that wherever this table is printed it should carry the addition Visual acuity to be assessed with best *wearable* glass

Furthermore it should be stressed that in Denmark at least the table is a *minimum* table i e there can be a question only of *raising* the percentage This applies in exceptional cases where special conditions make it reasonable to deviate from the tabular rate especially when the victim s occupational education and usual occupational field require a visual acuity above average

Graphically the current Scandinavian table was compared with older and more

S	6/6	6/12	6/18	6/24	6/36	6/60	2/60	0
6/6	0	0	5	8	10	12	16	20
6/12	0	5	10	10	12	15	18	20
6/18	5	10	20	25	30	35	40	45
6/24	8	10	25	35	45	50	55	60
6/36	10	12	30	45	55	65	70	75
6/60	12	15	35	50	65	75	80	85
2/60	16	18	40	55	70	80	95	100
0	20	20	45	60	75	85	100	100

Current interscandinavian normal table for assessing disability due to unilateral and bilateral impairment of central vision following eye injuries

Alberth B Surg cal treatment of caustic injuries of the eye Akademiai Kiado Buda pest 1968 147 pages in English illustrated Price $ 7.50

The monograph is based on the experiences from more than 1400 keratoplasties in the University Eye Clinic of Debrecen It deals with the least prosperous group in kerato plasty e g total leukoma extensive symblepharon invading the cornea and xerophthal mia Particularly severe lime burns have contributed to the group

In 1961 the author published a monograph on keratoplasty and the general problems are discussed again with regard to the progress made since then Lamellar transplanta tion is preferred eventually repeated several times Steroids are given orally and locally for six weeks if the recipient cornea is vascularized and immunosuppression with 6 mercaptopurine is added according to promising results in own experimental rabbit series

In the surgical management of sym and ankyloblepharon the value of auto haemo injection subconjunctivally is emphasized as part of the surgical treatment

This haemoinjection is also beneficial in severe acute lime burns combined with lamellar keratoplasty a chaud Not only therapeutic, but also optical results were obtained in 21 of 27 operations performed à chaud Prior to these operations experi mental work had demonstrated that the theory of a long acting depot of the caustic material in the eye does not hold It is not the lime but the degree of corneal damage caused by it which is responsible for the unfavourable consequences ensuing later

Many excellent illustrations and tables including many patients serve as documenta tion for the therapeutic results Severe caustic injuries seem to be more frequent in Hungary than in danish eye clinics It can therefore be recommended to seek inspira tion in this monograph *H Fledelius Copenhagen*

Seit R Klin k und Pathologie der Netzhautgefasse Enke Verlag Stuttgart 1968 459 pages 464 illustrations 16 of which are in colour Price 114 DM

This admirable monograph is based partly on the authors results in a thorough study of the retinal vessels in healthy and diseased eyes comparing the ophthalmoscopic fundus changes with the histopathologic findings in the same subjects which were published in Die Netzhautgefasse in 1962 and partly based on further investigations using the same technique

The book appears as a textbook as well as a manual and is divided into a general and a special part

In the first part the author in general discribes vascular alterations of the retinal vessels including crossing phenomena by comparing specimens clinically and histo pathologically

In the second part there is a clinical and histopathological description of vascular changes in arteriosclerosis hypertension, occlusion of retinal artery and vein, angio-matosis of the retina Eales disease and in a number of systemic diseases including diabetes and blood diseases

It is pointed out that no vascular reaction is pathognomonic of a single disease or a characteristic reaction solely of the retinal vessels.

ment with a view to postponing the decision or possibly to resuming the case at the end of 5 years

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Discussion *H Ehlers H Skydsgaard V Clemmesen S Ry Andersen Viggo A Jensen G Pouplier K Mellemgaard*

H Ehlers The public authorities should give an insured person full compensation also for reduced working ability The fact that the victim has suffered a loss also in the form of a greater risk should the other eye sustain an accident is not considered primarily However public insurance continues and affords compensation if this risk does arise It is different with private insurance which perhaps has been discontinued at the time that the other eye sustains an injury This should be borne in mind by the ophthalmologist as lawyers and insurance companies often merely refer to the official compensation tables

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S E Lorent en was presented with the *Gregg pri e* by the Australian consul *E H Hanfield* at the Nyborg meeting on May 4th 1968

Niels Ehlers was presented with Direktor Rasmussens legat by Professor V *A Jensen* at the meeting of the Swedish Ophthalmological Society in Lund on May 25th

Professor Holger Ehlers was awarded the *Professor Hjalmar Schiøt memorial medal* at the spring meeting of the Norwegian Ophthalmological Society in Tønsberg 1968

R M Fasanella Komplikation in Augenchirurgie und ihre Behandlung 1968 Ferdinand Enke Verlag 592 pages DM 116 –

This is a German translation by Professor H Hofmann of the second edition of Fasanella's Management of Complications in Eye Surgery 1957 In collaboration with a score of experienced ophthalmic surgeons Fasanella has rendered a thorough presentation of the pitfalls which may lead to complications as well as the management of the difficult situations which may arise in the course of numerous procedures In the present German edition the number of authors has been increased to give recent advances within ophthalmic surgery

The book is divided into 25 chapters starting with a description of anaesthesia complicating medical and psychiatric diseases Each chapter comprises valuable instructions concerning the correct preparation and technique of the various operations but many subjects appear to be described in too much detail for Scandinavian ophthalmologists who generally have access in the hospitals to the needed expert assistance within the various auxiliary disciplines

The section on intraocular foreign bodies lacks the planostereoscopic X ray technique utilizing an image amplifier described by Ratjen, which is the gentlest and most accurate existing method of location I have been using it successfully in collaboration with Ratjen during the past ten years The conventional methods of X ray location often prove of no value in the presence of foreign bodies lying mobile in the vitreous body e g shots splinters of cartridge cases and the like

In connection with the aspiration technique in congenital cataract the book mentions the two way syringe which regrettably seldom functions satisfactorily By simultaneous injection of saline solution through a thin needle and aspiration by a thick needle the depth of the anterior chamber may be regulated and the lens parenchyma as well as the capsule are easy to remove for instance with the double needle (Ferguson Bruun Jensen)

Cryoextraction of cataract is described by Krwawicz who restricts himself to his own technique not mentioning others

The complications of operations for retinal detachment are numerous and are accordingly described in great detail but nevertheless in a perspicuous manner

The book gives the all round ophthalmic surgeon an extremely valuable orientation in preventing and treating the complications which regrettably do not always receive sufficient attention in ophthalmosurgical literature

Viggo A Jensen

A Urrets Zavalia Jr Le decollement de la rétine Masson et Cie Paris 1968 Pp 713 314 figures 8 colour plates Price 230 NF

Like so many fields of ophthalmology retinal detachment is being discussed in an ever increasing number of publications not only case reports but also compilations from colloquia and congresses A detailed knowledge of and a collected view of this immense quantity of experience and reports can be gained only by a few who take a particular interest in the subject It is to be welcomed therefore that as a link in the current series of compilations on selected ophthalmological main subjects issued by

The text is illustrated by fundus photographs and microphotos in black and white and by some instructive drawings in colour

It is a valuable book for the ophthalmologist

Hans Walther Larsen

Brauner F & Brauner A Examen de l acuité visuelle Les Editions Sociales Francaises Paris 1968

These authors have published charts for testing the visual acuity of children who are too young to read or who are mentally deficient The charts are intended for use at a distance of 4 m and have been worked out with a particular view to determining refraction They are graduated according to the decimal system

The testing of vision in children of these categories is difficult and new aids are to be welcomed *Holger Ehlers*

Kienle G Die optischen Wahrnehmungsstorungen und die nicht euklidische Struktur des Sehraumes IV 172 pages 130 figures 44 tables DM 48 Georg Thieme Verlag Stuttgart 1968

The perception of optically recognized objects is not always explicable physically according to Euclidean geometry Hyperbolic geometry offers certain interesting possibilities which according to the author may be transferred to the visual space (Sehraum")

After reviewing the literature on disturbances in visual three dimensional perception, the author reports his experiments concerning the axiom on the parallel lines and a number of horopteric experiments The author who is a neurologist takes novel views of the classical physiological optics views which set an ophthalmologist thinking

Holger Ehlers

F Hervouet Travaux d Anatomie Pathologique oculaire Quatrième Série Masson et Cie Paris 1968 Pp 166 213 photomicrographs by M Ertus

This is the 4th series of ophthalmopathological papers from the Laboratoire de la Clinique Ophtalmologique de Nantes It comprises partly pathological studies of major series of well known diseases and partly reports of more rare cases – In particular it is worth emphasizing the study of the diabetic eye and a thorough description of the various types of uveitis

The papers are accompanied by black white photos of light microscopic sections

The book is characterized not only by the special French nomenclature but also by the authors frequently very personal views

It may be of interest to ophthalmologists but particularly to ophthalmic pathologists

O A Jensen

A Herrmann Gefahren bei Operationen an Hals Ohr und Gesicht und dit Korrektur fehlerhafter Eingriffe Springer Verlag Berlin – Heidelberg – New York 1968 733 pages Price DM 298 US $ 74 50

The author who heads the University E N T Clinic in Munich reports 40 years operative experience In addition to what is expected of an elementary textbook all 1ↄ sections emphasize what is in the author s opinion the correct method while other procedures are criticised Errors are often tactfully referred to as what the young surgeon would do The idea of this form of presentation is interesting in so far as it gives a picture of an industrious and conscientious authoritarian university teacher with a subjective attitude to the problems of his discipline

In view of the increasing practice of bringing actions for damages against German clinics the authors feels according to his preface that the book meets an urgent need However it is perhaps questionable whether it is beneficial to study the sources of error with such thoroughness Only part of the subject matter will be remembered and perhaps not always the correct part In the brief sections where plastic surgery is mentioned the description bears witness to limited experience with the exception of the section on facial palsy No mention is made of the surgery of the orbit or the surroundings of the eye There is a comprehensive bibliography and subject index The book is too expensive

Michael Pers

La Societe Francaise d'Ophthalmologie Urrets Zavalia has taken upon himself the enormous task of rendering a collected presentation of the problems concerning idiopathic retinal detachment

To illustrate the various aspects he divides the book into 5 main sections The first 3 deal with the conditions which lead to retinal detachment, the mechanism of the detachment including a thorough description of the ruptures and their role, and the clinical appearance of manifest retinal detachment

The last 2 sections comprise partly diagnostic methods and procedures partly surgical treatment its technique indications complications and results

On the basis of an enormous number of facts and clinical observations collected by perusal of practically the entire literature the author gives a consecutive presentation of the extremely complicated details laying particular stress upon a close relationship between the individual clinical features the preclinical condition choice of operation and operative result

Each section is accompanied by a comprehensive bibliography so that the reader can easily find the author s sources

This impressive work supplies a long felt need to those who want a collected presentation of the problems relating to retinal detachment The book is extremely well planned The illustrations are good and the presentation is easily understood and clear in spite of the abundance of detail

Of course it is not suitable as reading matter for every ophthalmologist but as a work of reference for those who wish to acquire a profound knowlegde of this fascinating disease It ought to be available in any ophthalmic library

Jens Edmund

Documenta Ophthalmologica Vol 24 1968 IV + 412 p 107 figures and 2 colour plates Dutch guilders 75 Dr W Jung Haag 1968

Thirty years have passed since the Documenta Ophthalmologica started appearing To secure a quicker publication of the articles the Documenta for 1968 are being issued in fascicles

Vol 24 No 1 brings the following papers

Wichser J Basle Kristalline Einlagerungen im Glaskorper

Fisher R F London The Variations of the Peripheral Visual Fields with Age.

Riaskoff S Essen Zur Immunogenese und Immunodiagnostik der endogenen Uveitis

Roth A Strasbourg Le sens chromatique dans l amblyopie fonctionelle etude clinique avant et au cours de la réeducation

Vol 24 No 2 brings the following papers

Utermann D & J J Klempien Hamburg Über Beziehungen zwischen den Erscheinungsformen der Arteriosklerose am Augenhintergrund und degenerativen Erkrangungen am allgemeinen Gefasssystem

Bock J & F Feyrter Vienna Über das interzellulara Interstitium des sog Mischtumors der Tranendrusen

Hayreh S S London Pathogenesis of Oedema of the Optic Disc

Holger Ehlers

12 Jahreshauptversammlung der Österreichischen Ophthalmologischen Gesellschaft in Wien 5-8 6 1968

Gleichzeitig finden ebendort zwischen dem 2 und 7 6 1969 das 3 Internationale Symposium uber Ultraschall Diagnostik in der Ophthalmologie SIDUO III und die Internationale Tagung uber Ultraschalldiagnostik in der Medizin statt die ophthalmologische Echographie wird am 4 und 5 6 1969 besprochen

Anfragen und Anmeldungen sind an Doz Dr W Funder erbeten, Wiener Medizinische Akademie fur arztliche Fortbildung Spitalgasse 2 A 1090 Wien IX. Österreich.

Sprechzeit Vortrage 10 Minuten Mitteilungen und Demonstrationen 6 Minuten.
Anmeldeschluss fur wissenschaftliche Beitrage 1 3 1969

A 5 days International Symposium on Fluorescein Angiography is held June 9 14 1969 Albi France

For all information and inscription
Pierre Amalric M D Centre Ophtalmologique 81 Albi France

The seventh Symposium of the International Society for Clinical Electroretinography (ISCERG) will be held September 14 to 18 1969 in Istanbul Turkey

Papers are solicited covering various aspects of electrophysiology and pathology of the visual system Further information may be obtained from
Professor Demir Basar Capa Goz Kliniği Istanbul Turkey
Registration fee
$ 20 00 for ISCERG members
$ 25 00 for participants non members of ISCERG
$ 10 00 for family members

3rd International Conference on Congenital Malformations

Netherlands Congress Centre
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7-13 September 1969

Secretariat before and after the Conference
c/o Holland Organizing Centre 16 Lange Voorhout, The Hague the Netherlands

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Interesting Cooperation Between Scandinavian Illuminating Engineering Laboratories

The illuminating engineering laboratories of the technical universities in Norway Sweden and Denmark have instituted a cooperation In addition to these 3 laboratories the illuminating engineering branch of the control laboratories of the Norwegian board for approval of electrical equipment (NEMKO) and of the Oslo power stations are partners in the cooperation and the state testing laboratory in Sweden participates in certain fields

The object of this cooperation is to secure the best possible coordination in photo metric methods and research within illuminating engineering to avoid unnecessary overlapping of the activity In addition the inspiration afforded by the close contact will naturally be of great importance to the individual laboratories

The first practical results of the cooperation are available already To obtain uni form measurements of lighting fittings a number of photometric measurements have been done on two separate fittings in the illuminating engineering laboratory Den mark and the laboratory measurements will be reported in Norway and Sweden The results are later to be compared and discrepancies if any will be investigated

Furthermore a proposal for Scandinavian standards for photometry of lighting fittings has been discussed and sanctioned with few amendments It is planned to publish these standards as national codes of practice in Sweden and Denmark and to publish the standards as recommendations in Norway

The advantage of these Scandinavian standards is evident

The next problem to be discussed is the measurement of retro reflecting materials used for road signs and for reflector devices on motor vehicles

On the whole great expectations are being entertained in respect to this new coope ration Its results ought to be to the benefit not only of the laboratories themselves but also of the consumers manufacturers of lighting fittings power stations etc

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New Delhi – 1 (India)

ORBITAL AFFECTION IN NASAL AND PARANASAL NEOPLASMS

BY

HARI MOHAN F R C S D K. SEN M S and D K GUPTA M S

Introduction

Neoplasms of the nose and paranasal sinuses affecting the orbit comprise a heterogenous group which are encountered quite infrequently by the average practising ophthalmologist Though such neoplasms usually affect the orbit in the late stages involvement of it at an early stage is not unknown The prognosis is much better where the orbital involvement is merely due to associated inflammatory reaction but in most cases the tumours grow to encroach upon the orbit or actually involve the orbital tissues

Eye findings are not only indicative of the extent but also of the site of the primary lesion which itself may be inaccessible to clinical examination

In some cases the orbital involvement is as a result of treatment of the tumour surgical or irradiational and it is the duty of the ophthalmologists to apprise their E N T colleagues of such post operative and post radiational orbital and ocular complications that may accrue eventually

Present study

This report is concerned with a series of 31 cases who attended this Hospital over a period of six years In all the cases diagnosis was established by clinical

Received May 31st 1968

Table I
Age and Sex distribution

Sex		0–20 Yrs	21–30 Yrs	31–40 Yrs	41–50 Yrs	51–60 Yrs	Over 60 Yrs	Total
Male	Malignant	0	2	2	5	4	0	13
	Benign	2	0	0	1	0	0	3
Female	Malignant	0	0	2	6	0	3	11
	Benign	2	1	0	1	0	0	4
Total		4	3	4	13	4	3	31

radiological and histopathological examinations The site and extent of the lesions were carefully assessed at operation when undertaken

Table I reveals overall maximum incidence in the age group of 41 50 years constituting 42 % Benign tumours were commonly found to be occurring in the first two decades and malignant tumours in the age group of 41 50 years Males were found to be suffering from malignancy slightly more than females (13 out of 24 cases) In the benign group number of males and females was al most equal

Table II shows that females were predominant (10 out of 16 cases constitut ing 62 5 %) so far as the ethmoidal region is concerned but the reverse was true (7 males out of 11 cases constituting 63 6 %) in the maxillary region In the nose the ratio of males to females was 3 1

Table II
Region wise sex distribution

	Male	Female	Total
Ethmoidal sinus	6	10	16
Maxillary sinus	7	4	11
Nose	3	1	4
	16	15	31

Table III
Type and site of origin of tumour

	Maxillary	Ethmoid	Nose	Total
Benign				
Fibrous dysplasia	0	6	0	6
Xanthogranuloma	1	0	0	1
Malignant				
Carcinoma				
Undifferentiated	3	2	0	5
Squamous celled	5	6	3	14
Anaplastic – transitional	0	1	0	1
Lymphosarcoma	2	0	0	2
Fibrosarcoma	0	1	0	1
Haemendothelioma	0	0	1	1
Total	11	16	4	31

Table IV
Ocular manifestations

	Maxillary Tumour	Ethmoidal Tumour	Nasal Tumour
Defective vision	3	4	0
Epiphora	4	2	1
Neuralgia	3	4	2
Congestion of conjunctiva	2	3	0
Restriction of ocular movement	3	5	2
Proptosis	9	6	3
Lateral displacement	[illegible]	10	2
Down displacement	0	2	0
Up displacement	10	0	2
Pallor of optic disc.	1	1	0
Papilloedema	2	1	0

The various types of tumours affecting the different regions are tabulated (Table III) It is obvious that the majority (24 out of 31 cases) were malignant tumours, carcinoma being the commonest (20 out of 24 cases) In the benign group all excepting one were fibrous dysplasias It is also evident that the ethmoidal region accounted for 51 6 % of cases (16 out of 31 cases) All the benign tumours excepting one had their origin in the ethmoid

Among ocular manifestations (Table IV) displacement of the globe and proptosis were most frequent Restriction of ocular movements though present was not associated with ophthalmoplegia Papilloedema was seen in 3 cases and optic atrophy in two In 9 cases the patient had moderate to severe neuralgic pain Unilateral epiphora was present in 7 cases It was interesting to note that in 3 cases of maxillary carcinoma epiphora was the initial symptom

Table V indicates that surgical intervention cured all the cases of fibrous dysplasia Radiotherapy did not cure carcinomas in very advanced stage as the patients reported quite late but offered relief of symptoms with regression of the tumour in 12 cases One case was cured by radiotherapy combined with conservative surgery of palatal fenestration and two cases improved with this

Table V

Response to various therapy

	Radiotherapy			Surgery			Combination			Total
*	C	I	F	C	I	F	C	I	F	
Benign										
Fibrous dysplasia	–	–	–	6	–	–	–	–	–	6
Xanthogranuloma	1	–	–	–	–	–	–	–	–	1
Malignant										
Carcinoma										
Maxillary	–	4	2	–	–	–	1	1	–	8
Ethmoidal	–	6	2	–	–	–	–	1	–	9
Nose	–	2	1	–	–	–	–		–	3
Lympho sarcoma	–	–	2	–	–	–	–	–	–	2
Fibro sarcoma	–	1	–	–	–	–	–	–	–	1
Haemendothelioma	–	1	–	–	–	–	–	–	–	1
	1	14	7	6	–	–	1	2	–	31

* C = Cured
I = Improved
F = Failed

procedure The cases of fibrosarcoma and haemendothelioma were relieved considerably by radiotherapy This state of regression is being maintained for last two years

Discussion

Tumours of the nose and paranasal sinuses affecting the orbit are not common The incidence in this hospital was one in 7542 patients attending eye out patient department and one in five proptosis cases

The age incidence rose sharply after the age of 40 years and then declined which corresponds well with the age incidence of most other malignant tumours

The incidence of malignant tumours in the nose and paranasal sinuses is usually said to be higher in males than in females *Ohngren* (1933) gave the incidence as 20 males to 17 females and *Windeyer* (1943) found 20 males to 18 females *Ballenger* (1947) put the ratio as high as 7 1 but *Capps* (1950) recorded the incidence as 36 males to 35 females In our series of 24 cases there were 13 males This fluctuation suggests that there may be nothing particular in the sex incidence The view that like some other neoplasms malignancy here is becoming more common in females is not acceptable

Of all the sinus carcinomas that in the antrum was found to be the commonest to invade the orbit (*Puccioni* 1899 *Johnston* 1906 *Shoda* 1925 *Harmer* 1935 and *Forrest* 1949) However we found the incidence almost equal with the antral and the ethmoidal humours

New (1938) stated that the squamous cell type of carcinomas formed a much higher proportion than it was described formerly and attributed this to a change in the view point of the pathologists *Windeyer* (1943) *Capps & Williams* (1950) supported New in his contention In our series also the commonest tumour was found to be the squamous cell type of varying degrees of differentiation (14 cases out of 20) *Fuing* (1940) considered these tumours to arise from the metaplastic epithelial lining

It is to be noted that inspite of the anatomic distortion there was rarely any interference with the visual acuity and visual fields in those cases where fundi were normal Optic atrophy and papilloedema are not very common but may be present due to retro bulbar and/or intracranial extension

Epiphora in an elderly patient should always excite suspicion X ray examination of the lacrimal sac and nasolacrimal duct after injection of lipiodol is helpful in such cases If epiphora is associated with hyperaesthesia hypoaesthesia or anaesthesia of the region supplied by the infraorbital nerve and not associated with any positive clinical E N T finding a Caldwell Luc operation

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and direct visualization is advocated, even if radiological findings are negative

Proptosis is almost always a late phenomenon and may be due to retrobulbar involvement or displacement of any of the orbital walls or mucocele developing secondary to obstruction to drainage from the sinuses In the latter event the primary growth may be missed and a wrong diagnosis of an innocent mucocele may be made

Surgery remains to be the procedure of choice in benign neoplasms In treating malignant tumours one should remember that pure surgery is now a thing of the past and irradiation by itself is inadequate in so far as post irradiation drainage and subsequent follow ups are concerned A combination of surgery, limited or radical, and irradiation therefore gives the highest proportion of success The sequence of measures adopted were intranasal antrostomy followed by irradiation of about 6000 r over a period of about 6 weeks followed by palatal fenestration and provision of a prosthesis In late stages however, extensive and mutilating operations were avoided and radiotherapy resorted to as a palliative measure

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4 *Ewing J* Neoplastic diseases Ed 4 Philadelphia Saunders (1940)

5 *Forrest* A of O XLI (1949) 198 – cited by Duke Elder 1952

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8 *Johnston* O Rec *XV* (1906) 421 – cited by Duke Elder 1952

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13 *Windeyer B W* Skinner lecture Brit J Radiol *16* (1943) 362

Aus den Universitäts Augenkliniken
von Turku Finnland und Bern Schweiz

DER EINFLUSS VON LINSEN AUF DAS SCHALLFELD

Experimentelle Untersuchungen mit Schweinelinsen

VON

A. OKSALA (TURKU) und P. BLOK (BERN)

Der Ausgangspunkt für diese Untersuchungen war die Frage wie sich das Schallbündel verhält wenn es
a) senkrecht zum Linsenäquator und axial geführt wird und
b) durch Kippen des Schallkopfes nur um 1° und 2° exzentrisch durch die Randpartien der Linse hindurchgeht

Anordnung der Experimente

Es wurde das Impuls Echo Gerät Serie 7000 der Firma Kretztechnik verwendet Für eine möglichst genaue Messung wurde der Apparat mit einem Tektronix Oszilloskop Typ 515 A parallel geschaltet das eine feinere Ablesung der Echohöhen auf seinem Bildschirm gestattet.

Wir verwendeten weiter die von der Firma Kretztechnik gelieferten Schallköpfe mit den Frequenzen 6 MHz Ø ≈ 5 mm und Ultrasonolux 12 MHz Ø = 2 5 mm Der Schallkopf wurde für die ganze Dauer eines Experimentes in einem Behälter justiert Dieser Behälter kann senkrecht (= 0° Stellung oder Ausgangsstellung) gestellt werden und in zwei Richtungen (innerhalb einer

Die Arbeit wurde vom U S Public Health Service Grant NB 03659 07 vom National Institute of Neurological Diseases and Blindness Bethesda (USA) unterstützt.
Vorgetragen auf dem zweiten Kongress der SIDUO in Brno Mai 196
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Vorgetragen auf dem zweiten Kongress der SIDUO in Brno, Mai 1967.

Eingegangen am 9. September 1968.

Ebene) gekippt werden um einen Winkel, der auf einem Gradbogen ablesbar ist Die Achse des Schallbündels bewegt sich dabei in einer Ebene senkrecht zum Wasserspiegel

Eine Stahlkugel mit Ø = 1 mm und eine mit Ø = 1 5 mm (für die Experimente mit Schallkopf 6 MHz resp 12 MHz) als echogebendes Objekt wurden in dieser Ebene horizontal durch das Schallfeld (im Wasserbad) geführt und zwar 15 mm 20 mm und 25 mm vom Mittelpunkt des Schallkopfes entfernt Die Stahlkugel ist oben auf eine senkrecht stehende Nadelspitze geleimt Die Stellung dieser Kugel kann fortlaufend bis auf 0 1 mm genau abgelesen werden und ist beliebig reproduzierbar Auch die Einstellung des Abstandes zwischen Testkugel und Kristallmitte ist bis auf 0 1 mm genau möglich und reproduzierbar

So konnte die Breite des Schallfeldes in den angegebenen Entfernungen vom Schallkopf festgelegt werden und die in diesen Strecken vorkommenden Intensitätsmaxima und minima konnten in relativen Skalenteilen der Echohöhe lokalisiert werden Die so erhaltenen Zahlenwerte von Echohöhen (vertikale Achse) und Lokalisation in den obengenannten Strecken (horizontale Achse) wurden in Kurven aufgezeichnet wie auch die Werte die bei gleicher Anordnung doch bei Kippen des Schallkopfes in die Stellungen 1° und 2° nach rechts und nach links erhalten wurden Wir bezeichnen diese relativen Schalldruckkurven weiterhin als Blankokurven"

Die gleichen Experimente wurden dann wiederholt nachdem eine Schweinelinse zwischen Schallkopf und Testkugel geschaltet worden war Der vordere Linsenpol ist 4 mm vom Schallkopf entfernt und auf diesen in seiner Ausgangsstellung (0°) zentriert Der Linsenäquator – markiert durch feine Franzen Uveagewebe die beim Auspräparieren der Linse in situ gelassen wurden – wurde in zwei Richtungen möglichst genau parallel zum Wasserspiegel gebracht und die Linse somit möglichst horizontal gestellt

Während des ganzen Experimentes wurde diese Stellung unverändert beibehalten Probeweise wurden am Ende eines Experimentes 6mal an willkürlich gewählten Messpunkten die Ablesungen wiederholt Die Differenzen schwankten zwischen der ursprünglichen und der nachträglichen Ablesung zwischen 0 0 mm und 0 3 mm Ein Ablesungsfehler überschreitet also durchschnittlich nicht den Wert von 0 15 mm

Die aus diesen Experimenten erhaltenen Zahlenwerte wurden ebenfalls in Kurven aufgezeichnet wie es die Abb 1 und 2 zeigen Wir sprechen von diesen Kurven kurzweg als "Ls Kurven

Es wurde eine Versuchsserie mit dem Schallkopf 6 MHz und 4 Linsen gemacht anschliessend eine 2 Serie mit dem Schallkopf 12 MHz und 4 anderen Linsen Der Leistungsregler des Geräts war mit einer db Skala 0–70 versehen und die gewählte Leistung in der ersten Serie betrug 20 db Reserve wenn Schallkopf und Testkugel 15 mm voneinander entfernt waren und 10 db

Reserve bei den Entfernungen 20 mm und 25 mm In der 2 Serie wurde die Leistung 5 db Reserve gewahlt weil mit hoherer Frequenz die Absorption durch die Linse stark zunimmt

Messergebnisse

Die mit der oben angegebenen Methode gemachten Messungen sind in den Abb 1 und 2 in Kurven verarbeitet die für jede Linse mit einer eigenen Linien charakteristik gezeichnet worden sind Die Blankokurven sind erkennbar durch ihre hoheren Spitzen und ihre Gleichformigkeit

Die Kurven sind fur die Entfernungen 15 mm 20 mm und 25 mm uberein ander gezeichnet damit die Divergenz und die Brechung des Schallbundels durch die Linse sofort ersichtlich werden Auf die horizontalen Achse ist zwischen den Fusspunkten einer Kurve die betreffende Breite des Schallfeldes – in diesem Meridian gemessen – abzulesen Auf diese Achse projiziert konnen die Spitzen der Kurven in ihrer horizontalen Lokalisation miteinander ver glichen werden Auf der vertikalen Achse wie oben besprochen sind die Echohohen angegeben

Die Diameter der gebrauchten Linsen (in der aquatorialen Flache gemessen) und ihre Dicke (gemessen zwischen vorderem und hinterem Pol) findet man in der Tabelle 1 angegeben Die L_1 und L_4 in der ersten Serie zeigen in den Stellungen 0° und 1° des Schallkopfes ein grosseres Absorptionsvermögen als L_2 und L_3 Ob dieses evtl mit der langeren Zeit nach dem Schlachten des Tieres zusammenhangt ist nicht untersucht worden In der zweiten Serie ist es gerade die 9 Stunden alte Linse L_2 die am wenigsten Energie absorbiert hat und die hochsten Kurvenspitzen in den Stellungen 0° und 1° des Schallkopfes zeigt Die Linsen wurden im Kuhlschrank aufbewahrt

Diskussion

Über die Breite des Schallbundels dessen Verlauf in den Kippstellungen des Schallkopfes und uber die Verteilung der Schalldruckintensitat innerhalb des Bundels ohne den Einfluss der Linsen informieren uns die Blankokurven" Zu diesen Kurven (vgl Abb 1 und 2) sind folgende Bemerkungen zu machen 1 Die 5 Blankokurven die man fur gleiche Entfernung Schallkopf – Test kugel erhalt sind fur einen und denselben Schallkopf einander sehr ahnlich

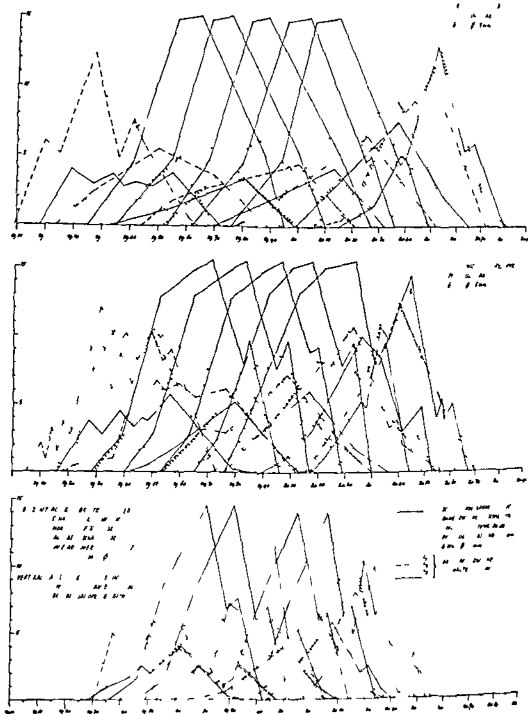


Abb 1
Die Blankokurven und Ls Kurven mit dem Schallkopf 6 MHz und in drei Entfernungen gemessen

Kleine Differenzen entstehen durch minimale Entfernungszunahme Schallkopf – Testkugel in den Stellungen 1° und 2° und durch Ablesungsfehler

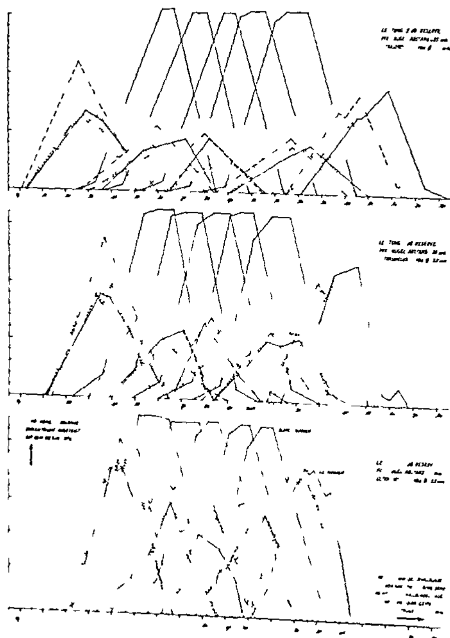


Abb. 9

Die Blankokurven und Is-Kurven mit Ultrasonolux (1? MHz) und in drei Entfernungen gemessen

Tabelle 1

		Ø	Dicke	Zeit in Std nach Schlachtung des Tieres bei Anfang des Experimentes
Serie I	I_1	9 7 mm	8 4 mm	24
	L_2	9 5 mm	8 1 mm	2 5
	L_3	9 8 mm	8 2 mm	5
	L_4	9 7 mm	8 3 mm	24
Serie II	L_1	9 7 mm	8 3 mm	6
	L_2	9 8 mm	8 3 mm	9
	L_3	9 7 mm	8 3 mm	11
	L_4	9 9 mm	8 2 mm	7

2 Die Einstellung des Schallkopfes in 0° 1° usw wurde fur die Blanko Versuche von freiem Auge und nur einmal gemacht und zwar mittels eines Gradbogens mit sehr feiner Skalenteilung Das erklart die nicht immer ganz gleichen Entfernungen zwischen den Kurvenspitzen

3 Die Basisbreiten in den Experimenten mit dem Schallkopf 6 MHz sind in der Entfernung von 20 mm deutlich grosser als in der Entfernung von 15 mm doch diese Differenz ist auf den Leistungsunterschied 10 db Reserve / 20 db Reserve zurückzufuhren Die Lage der Kurvenspitze wurde dadurch aber *nicht* beeinflusst

4 Die senkrechte Justierung des Schallkopfes Ultrasonolux 12 MHz erfolgte optisch mittels der sichtbaren Metallachse Die Testkugel wurde in dieser Achse justiert und weiterhin nur noch in einer Ebene die diese Achse enthalt horizontal durch das Schallfeld gefuhrt 15 mm 20 mm und 25 mm von der Schallkopfmitte entfernt Die Verschiebung der Intensitätsmaxima der Blankokurven" in der 0° Stellung erfolgte in den Entfernungen 15 mm → 20 mm → 25 mm nicht senkrecht doch schrag (in Abb 3 von links oben nach rechts unten) was dafur sprechen wurde dass entweder die Justierung ungenau war oder (und) dass die Schallbundelachse dieses Schallkopfes nicht mit der sichtbaren Metallachse zusammenfallt Dementsprechend ist die Gesamtrichtung aller in der Stellung ubereinstimmenden Intensitatsmaxima der Ls Kurven in der gleichen Abb 3 von links oben nach rechts unten verzogen aber der Einfluss der Linse kommt jedenfalls zum Vorschein Aus dem Verlauf der gestrichelten Linie in Abb 4 geht hervor dass die Achse des Schallbundels mit der Achse des 6 MHz Schallkopfes zusammenfällt bzw höchtens in der zu unserer Neigungsebene senkrechten Ebene von dieser Achse abweicht

5 Ohne zwischengeschaltete Linse verursachten die verwendeten Leistungen

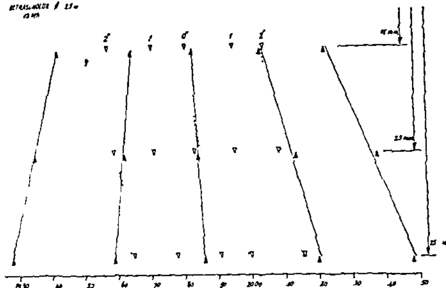


Abb 3

Die Stellungen der Intensitatsmaxima der Blankokurven und der Ls Kurven (die ausgezogene Linie) mit Ultrasonolux und in drei Entfernungen gemessen

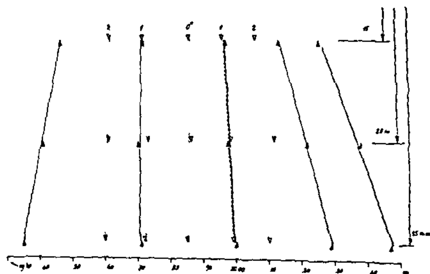


Abb 4

Die Stellungen der Intensitatsmaxima der Blankokurven und der Ls Kurven mit dem Schallkopf 6 MHz und in drei Entfernungen gemessen.

Tabelle 1

		Ø	Dicke	Zeit in Std nach Schlachtung des Tieres bei Anfang des Experimentes
Serie I	L_1	9 7 mm	8 4 mm	24
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3 Die Basisbreiten in den Experimenten mit dem Schallkopf 6 MHz sind in der Entfernung von 20 mm deutlich grosser als in der Entfernung von 15 mm doch diese Differenz ist auf den Leistungsunterschied 10 db Reserve / 20 db Reserve zurückzufuhren Die Lage der Kurvenspitze wurde dadurch aber *nicht* beeinflusst

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5 Ohne zwischengeschaltete Linse verursachten die verwendeten Leistungen

hoher werden muss der Energieverlust durch Reflexion klein sein im Verhaltnis zu dem gleichzeitigen Energiegewinn durch geringere Absorption

2 Als Funktion der Frequenz

Mit Zunahme der Frequenz (Ultrasonolux" Schallkopf 12 MHz) musste auch die Leistung erhoht werden (bis auf 5 db Reserve) damit Kurven erhalten wurden die mit den Kurven aus dem Experiment mit Schallkopf 6 MHz vergleichbar sind Es nimmt also die Absorption des Ultraschalls durch die Linse mit Zunahme der Frequenz zu was schon fruher bekannt war Dieser Absorptionsvergleich ist nicht ganz genau schon wegen der verschiedenen Schallkopfdiameter

3 Als Funktion der Leistung

Die Blankokurven sind oben mehr oder weniger abgeflacht die vertikale Abbildungsgrenze auf dem Schirm ist erreicht Ein Vergleichen zwischen den Echohohen der Blankokurven und denen der Ls Kurven ist deshalb nicht exakt moglich Leistungseinstellungen die dieses moglich machen würden erwiesen sich als zu schwach um noch deutliche Ls Kurven zu registrieren

B Über die Brechung des Schallbundels durch die Linse *in unseren experimentellen* Aufstellungen informieren uns wiederum die Abb 1–7 In Abb 6 ist der Strahlengang aus den Kurven rekonstruiert und schematisch gezeichnet In Abb 7 sind ubersichtlichkeitshalber nur eine Blankokurve in 2° Stellung und die zugehorigen 4 Ls Kurven abgebildet. Man sieht nochmals deutlich die Verschiebung der Ls Kurven gegenuber der Blankokurve

Die Spitzen der Ls Kurven in 2° Stellung des Schallkopfes sind von den zugehorigen Blanko Spitzen in 2° Stellung weiter entfernt als die Spitzen der Ls Kurven in 1 Stellung von den zugehorigen Blanko *Spitzen in* 1° Stellung Betrachten wir dieses Phänomen in der Entfernung Schallkopf Testkugel = 15 mm (Ultrasonolux Abb 3) dann mussen wir die Distanz der Spitzen der Blankokurven in 1° und in 2° Stellung zu der Blanko Spitze in 0 Stellung mit einem Faktor ca 1 7 multiplizieren um die Distanz der zugehorigen Ls Spitzen zu der Blanko Spitze in 0° Stellung zu erhalten

Mit zunehmender Entfernung Schallkopf – Testkugel (20 *mm* 25 mm) wird dieser Multiplizierungsfaktor grosser was sich in Abb 3 als deutliche Divergenz der Strahlen im Vergleich mit dem Strahlengang in den Blanko Versuchen manifestiert Damit ist deutlich gezeigt dass die Rander der Linse die Ultraschallwellen bei der hier angewandten Strahlenrichtung starker brechen als die Linsenmitte In dieser Hinsicht verhalt sich die Linse wie eine Streulinse

C. Über die Form der Schalldruckkurven nach Durchgang durch die Linse ist zu sagen

1 In der 0 Stellung des Schallkopfes sind die Ls Kurven niedriger und weniger steil als in der 1° und in der 2° Stellung (siehe unter A Absorption)

Die Kurven sind annahernd *symmetrisch zur vertikalen Achse* Fur Abweichungen von dieser Symmetrie kommen in Betracht

Echohöhen die die Grenzen des Abbildungsbereiches des Bildschirmes uber schritten (mit Ausnahme der Leistungseinstellung 20 db Reserve) Demzufolge entstanden mehr oder weniger oben horizontal "abgeschnittene "Blanko kurven" Wir haben deshalb Spitzenmittelwerte pro Kurve *arithmetisch ermit telt*

Der Einfluss der *zwischengeschalteten* Linsen auf das Schallbündel kommt zum *Vorschein* in den "Ls Kurven" Wir können diese Modifikationen der "Blankokurven" folgendermassen *gliedern*

A Eine Absorption der Ultraschallenergie durch die Linse manifestiert sich

1 Als Funktion der *Linsendicke*

In Abb 5 ist die Modifikation des Schallfeldes durch eine Linse fur die Stel lungen 2°, 1° 0° 1° und 2° des Schallkopfes 6 MHz und für die Entfernung
↙ ↙ ↘ ↘
Schallkopf – Festkugel = 20 mm gezeichnet Die "Blankokurven" sind mit ausgezogenen die "Ls Kurven" mit gestrichelten Linien gezeichnet Die Lin senkurvenspitzen sind deutlich niedriger als die Blankokurvenspitzen Die Höhe der "Ls Kurven" nimmt zu mit dem Kippen des Schallkopfes Diese Ab hängigkeit wurde nur in einem Meridian untersucht, doch gilt für alle Meri diane dieses Schnittes prinzipiell das Gleiche

Die starke Absorption des Ultraschalls durch die Linse ist schon früher von Oksala und Varonen beschrieben worden und erklärt die niedrigeren Kurven spitzen in der 0° Stellung Ein Teil der Energie geht verloren z B durch Reflexion an den Linsenvorderflächen und -hinterflächen Dieser Teil nimmt zu bei schrägem Auffallen auf die Linse in den Stellungen 1° und 2° des Schallkopfes Da aber die Kurven in der Folge 0° 1° und 2°-Stellung immer

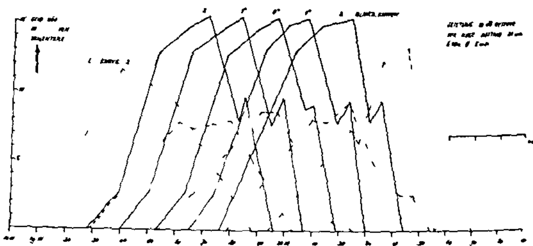


Abb 5
Die Modifikation des Schallfeldes durch eine Linse in 5 verschiedenen Stellungen

hoher werden muss der Energieverlust durch Reflexion klein sein im Verhaltnis zu dem gleichzeitigen Energiegewinn durch geringere Absorption

2 Als Funktion der Frequenz

Mit Zunahme der Frequenz (Ultrasonolux Schallkopf 12 MHz) musste auch die Leistung erhoht werden (bis auf 5 db Reserve) damit Kurven erhalten wurden die mit den Kurven aus dem Experiment mit Schallkopf 6 MHz vergleichbar sind Es nimmt also die Absorption des Ultraschalls durch die Linse mit Zunahme der Frequenz zu was schon fruher bekannt war Dieser Absorptionsvergleich ist nicht ganz genau schon wegen der verschiedenen Schallkopfdiameter

3 Als Funktion der Leistung

Die Blankokurven sind oben mehr oder weniger abgeflacht die vertikale Abbildungsgrenze auf dem Schirm ist erreicht. Ein Vergleichen zwischen den Echohohen der Blankokurven und denen der Ls Kurven ist deshalb nicht exakt moglich Leistungseinstellungen die dieses moglich machen wurden erwiesen sich als zu schwach um noch deutliche Ls Kurven zu registrieren

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C. Über die Form der Schalldruckkurven nach Durchgang durch die Linse ist zu sagen

1 In der 0 Stellung des Schallkopfes sind die Ls Kurven niedriger und weniger steil als in der 1 und in der 2 Stellung (siehe unter A. Absorption)

Die Kurven sind annahernd symmetrisch zur vertikalen Achse Fur Abweichungen von dieser Symmetrie kommen in Betracht

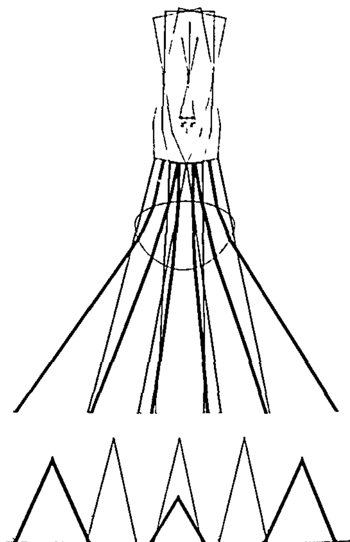


Abb 6
Der Einfluss der Linse (die dicke Linie) auf den Strahlengang schematisch gezeichnet

a) Die "Blankokurven" selber sind nicht streng symmetrisch
b) Akustische Inhomogenitaten der Linse
c) Siehe unter 3 (folgt)
d) Justierungsfehler

2 In der 0°-Stellung zeigen die "Ls Kurven" meistens nur 1 Intensitätsmaximum in der 1°-Stellung und noch deutlicher in der 2° Stellung mehrere Intensitätsmaxima die mit zunehmendem Abstand Schallkopf – Testkugel hinsichtlich der Anzahl abnehmen

3 In den 1° und noch deutlicher in den 2° Stellungen zeigen die "Ls Kurven eine Neigung in die Richtung in der das Kristall gekippt wird

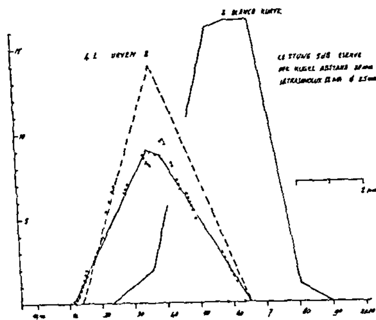


Abb 7

Eine Blankokurve in 2° Stellung und die zugehorigen 4 Ls Kurven

4 Wie aus den Abbildungen ersichtlich ist decken sich die Kurven mit je 4 Linsen weitgehend Am meisten ausgesprochen ist dies der Fall bei Verwendung des Ultrasonolux" Schallkopfes (fokussierter Strahlengang) Die 2×4 Linsen zeigen also eine weitgehend ubereinstimmende Brechung des Schallbundels und es muss eine weitgehende akustische Homogenitat in allen Meridianen einer Linse herrschen Es durfte denn auch der Mittelwert der Lokalisation der Intensitatsmaxima pro Kurve und pro Gruppe von 4 Kurven als reprasentativ fur die Modifizierung des Schallfeldes in allen Linsenmeridianen angesehen werden Diese ermittelten Lokalisationswerte sind in den Abb 3 und 4 mit dem Symbol ▲ angegeben.

D Die Zunahme der Basisbreiten mit Erhohung der Leistung (Exp Schallkopf 6 MHz Leistung 20 db Res → Leistung 10 db Res) kann aus der Zunahme von subliminalen Echos begriffen werden die jetzt zur Anzeige gelangen

Zunahme der Basisbreiten mit der Entfernung (20 mm → 25 mm) fur die Blankokurven in den Experimenten mit Schallkopf 6 MHz Leistung 10 db Res steht neben Abnahme derselben fur die gleichen Entfernungen in den Experimenten mit dem Ultrasonolux 12 MHz Leistung 5 db Res Fur die Ls Kurven ist diese Situation genau umgekehrt

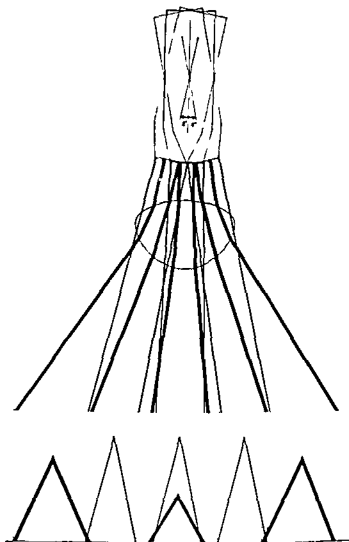


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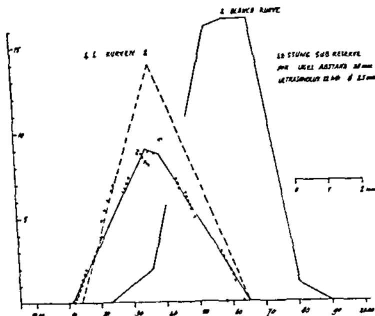


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Eine Blankokurve in 2° Stellung und die zugehorigen 4 Ls Kurven

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Die Basisbreite nimmt zu im Experiment mit Schallkopf 12 MHz bei Kippen in die 1°- und 2°-Stellungen und bleibt ungefähr gleich im Experiment mit *Schallkopf 6 MHz in diesen Stellungen mit dem Schallkopf 12 MHz wird in* der 0°-Stellung relativ mehr Energie von der Linse absorbiert als mit dem Schallkopf 6 MHz Dazu kommt wahrscheinlich noch der Faktor dass im fokussierten Feld die Messung der Basisbreite genauer und leichter ist

Ohne weitere Prüfung der Signifikanz dieser Differenzen bei verschiedener Frequenz und Leistung lässt sich hierüber nichts mehr aussagen

In unseren Experimenten ist die mit der Testkugel gemessene Schallbündelbreite (= Basisbreite einer Kurve) des "Ultrasonolux" Schallkopfes nachdem dem Schallbündel die Linse passiert hat in 25 mm Entfernung vom Schallkopf ca 5 mm Der Augenhintergrund wird Echos von geringer Intensität abgeben als es eine Stahlkugel tut Die registrierbare Schallbündelbreite kann also bei gleichbleibender Leistung am Augenhintergrund geringer sein Sie wird von Buschmann mit 1 2 mm angegeben

In den klinischen Untersuchungen mit diesem Schallkopf wird dessen konkave Fläche in bleibendem Kontakt mit der Hornhaut gehalten Kippbewegungen erfolgen mehr oder weniger um einen Drehpunkt = Hornhautkrümmungszentrum Die Schallbündelachse geht dabei stets annähernd durch das Zentrum der Linse Unsere Experimente sagen über die Brechung der Ultraschallwellen in diesen Kippstellungen nichts aus Es werden aber von der Hand des Untersuchers unvermeidlich auch Kippbewegungen gemacht die die Hornhaut deformieren und die unseren experimentellen Stellungen entsprechen

Der Abstand zwischen der Kippachse und dem Linsenvorderpol wurde für jeden Schallkopf konstant gehalten doch nicht genau gemessen Er beträgt ca 5 cm und ist grösser als der Abstand bei klinischen Untersuchungen (schätzungsweise ca 3 cm) In unseren Experimenten ist also der Effekt des Kippens etwas grösser als bei der klinischen Untersuchung Es sei noch erwähnt dass der Krümmungsradius der hinteren Linsenfläche im Schweine grösser als beim Menschen ist

Zusammenfassung

Um den Einfluss der Linse auf das Schallfeld im Auge unter einigen Bedingungen zu prüfen die bei der klinischen Untersuchung am Auge gegeben sind wurde in experimenteller Aufstellung dem nachgegangen wie der Strahlenverlauf des *Ultraschallbündels modifiziert wird* wenn es

a) Senkrecht axial auf die Linse auftrifft d h die Schallbündelachse durch Linsenvorderpol und -hinterpol geht

b) Aus dieser senkrechten Stellung durch Kippen uber 1° und 2° nach links und nach rechts gebracht wird

Der Verlauf der Strahlen wurde festgelegt mittels einer stahlernen Testkugel mit 1 mm und 1 5 mm O die in drei Entfernungen 15 mm 20 mm und 25 mm vom Schallkopf mitten durch das Schallfeld in einer geraden Linie senkrecht zur Schallbundelachse gefuhrt wurde wenn diese letztere in der 0° Stellung stand

Durch Vergleich des registrierten Strahlenverlaufs ohne und mit zwischen geschalteter Linse konnte festgestellt werden dass unter diesen Bedingungen der Linsenrand Ultraschallwellen starker bricht als die zentralen Linsenpartien Sie verhalt sich also fur Ultraschallwellen wie eine Streulinse

In den unter b) festgelegten Kippstellungen liegen registrierte Veränderungen am Augenhintergrund nicht mehr in der Verlangerung der Schallkopfachse was fur eine genaue Lokalisation der Befunde am Augenhintergrund wichtig ist

Litteratur

Buschmann W Ein neues optisch akustisches Untersuchungsverfahren Klin Mbl Augenheilk *14* 1 0–1 6 (1963)

Oksala A und *Lehtinen* *F P* Analysis of echoes from the rear eye wall with the aid of experimental and clinical research II Effect of the absorption of the lens and of amplification Acta ophthalm (Kbh) 4 92–93 (1964)

Oksala A und *Lehtinen* *E P* The effect of the lens on the ultrasonic field in diagnosis of the eye by ultrasound Acta ophthalm (Kbh) *43* 260–267 (1965)

Oksala A und *Lehtinen* *F P* The influence of the eyeball on the ultrasonic field of the transducer and its diagnostic significance Acta ophthalm (Kbh) *43* 963–971 196)

Die Basisbreite nimmt zu im Experiment mit Schallkopf 12 MHz bei kippen in die 1°- und 2° Stellungen und bleibt ungefahr gleich im Experiment mit Schallkopf 6 MHz in diesen Stellungen. Mit dem Schallkopf 12 MHz wird in der 0° Stellung relativ mehr Energie von der Linse absorbiert als mit dem Schallkopf 6 MHz. Dazu kommt wahrscheinlich noch der Faktor, dass im fokussierten Feld die Messung der Basisbreite genauer und leichter ist.

Ohne weitere Prüfung der Signifikanz dieser Differenzen bei verschiedener Frequenz und Leistung lässt sich hieruber nichts mehr aussagen.

In unseren Experimenten ist die mit der Testkugel gemessene Schallbündelbreite (= Basisbreite einer Kurve) des "Ultrasonolux" Schallkopfes nachdem dem Schallbündel die Linse passiert hat in 25 mm Entfernung vom Schallkopf ca. 5 mm. Der Augenhintergrund wird Echos von geringer Intensitat abgeben als es eine Stahlkugel tut. Die registrierbare Schallbündelbreite kann also bei gleichbleibender Leistung am Augenhintergrund geringer sein. Sie wird von Buschmann mit 1.2 mm angegeben.

In den klinischen Untersuchungen mit diesem Schallkopf wird dessen konkave Fläche in bleibendem Kontakt mit der Hornhaut gehalten. Kippbewegungen erfolgen mehr oder weniger um einen Drehpunkt = Hornhautkrümmungszentrum. Die Schallbündelachse geht dabei stets annähernd durch das Zentrum der Linse. Unsere Experimente sagen uber die Brechung der Ultraschallwellen in diesen Kippstellungen nichts aus. Es werden aber von der Hand des Untersuchers unvermeidlich auch Kippbewegungen gemacht, die die Hornhaut deformieren und die unseren experimentellen Stellungen entsprechen.

Der Abstand zwischen der Kippachse und dem Linsenvorderpol wurde fur jeden Schallkopf konstant gehalten, doch nicht genau gemessen. Er beträgt ca. 5 cm und ist grösser als der Abstand bei klinischen Untersuchungen (schätzungsweise ca. 3 cm). In unseren Experimenten ist also der Effekt des Kippens etwas grosser als bei der klinischen Untersuchung. Es sei noch erwahnt, dass der Krümmungsradius der hinteren Linsenfläche im Schweine grosser als beim Menschen ist.

Zusammenfassung

Um den Einfluss der Linse auf das Schallfeld im Auge unter einigen Bedingungen zu prufen, die bei der klinischen Untersuchung am Auge gegeben sind, wurde in experimenteller Aufstellung dem nachgegangen, wie der Strahlenverlauf des Ultraschallbundels modifiziert wird, wenn es

a) Senkrecht axial auf die Linse auftrifft, d. h. die Schallbundelachse durch Linsenvorderpol und -hinterpol geht.

sowohl die Absorption (Schwachung) des Ultraschalls in der Sclera und in der Cornea als auch die von diesen Geweben moglicherweise verursachte Brechung des Schallbundels bei Untersuchung aus verschiedenen Winkeln zu klaren Unter Absorption verstehen wir hier die auf unterschiedliche Weise erfolgte Verkleinerung des Schalldrucks und Verengerung des Schallfeldes im Vergleich zum Wasser

Die Untersuchungsgerate und das Material

Als Ultraschallgerat wurde der Apparat von Kretztechnik (Zipf/Oberösterreich) Modell 1000 benutzt Fur die Messungen der Amplituden der Echos wurde mit dem Ultraschallgerat ein Tektronix Oskilloskop 515 A verbunden Bei den Messungen wurde die Verstarkung immer gleich gross gehalten und zwar so dass das hochste Echo auf dem Schirm des Tektronix Oskilloskops die obere Mitte der Skala nicht uberstieg

Fur die Messungen des Ultraschallfeldes wurde ein Apparat gebaut bei dem der Schallkopf auf einem Stativ untergebracht werden konnte Unter dem Schallkopf in einer Wasserwanne wurde eine Stahlkugel von 1 5 mm Durchmesser bewegt und die Horizontal und Vertikalbewegungen dieser Kugel konnten auf der Nonius Skala mit einer Genauigkeit von 0 1 mm gemessen werden Aufgrund der Lage der Stahlkugel und der Amplituden ihrer Echos waren Kurven zu erhalten die fur die gewunschten Stellen des Schallfeldes den relativen Schalldruck anzeigten

Als Material wurden Schweineaugen verwendet die ein paar Stunden vorher enukleirt worden waren und die wir deshalb gewahlt hatten weil die Grosse dieser Augen und ihre intraokularen Distanzen – ausgenommen bei der Linse – stark ans Menschenauge erinnern Aus den Schweineaugen wurden zwei verschiedene Hullen prapariert von denen die eine die Sclera in der Gegend des Äquators und die andere die Hornhaut umfasste Die Dicke der Lederhaute betrug 0 6–0 9 mm und die der Hornhaute 1 4–1 6 mm Die Hullen wurden auf ein aus dunnem Kupferdraht angefertigtes Gestell gesetzt so das sie sich unter dem Schallkopf 5 mm von diesem entfernt befanden Bei der Untersuchung wurde ein einziger Schallkopf verwendet nämlich ein Ultrasonolux Schallkopf von 12 MHz und 2.5 mm der ein wenig fokusiert war (f = 17.5 mm) Dieser Schallkopf wurde deswegen gewahlt weil es bei einer derartigen Untersuchung vorteilhaft ist ein Schallbundel von verhaltnismassig geringem Durchmesser zu benutzen Die Untersuchungen wurden bei einer Temperatur von + 20 C ausgefuhrt

Aus der Universitäts Augenklinik Turku Finnland
(Direktor Prof Dr Arvo Oksala)

DER EINFLUSS DER AUGENHÜLLE AUF DAS SCHALLFELD

Experimentelle Untersuchungen mit Schweineaugen

VON

ARVO OKSALA und LEENA HÄKKINEN

Obgleich man in der Ophthalmologie schon über zehn Jahre lang experimentelle und klinische Ultraschallforschung getrieben hat sind die Angaben über das Verhalten des Ultraschalls im Inneren des Auges in verschiedenen Verhältnissen doch vielfach mangelhaft Am meisten hat man vielleicht die Schallgeschwindigkeit in den einzelnen Teilen des Auges untersucht aber auch diese unsere Kenntnis ist noch nicht in jeder Hinsicht genau genug

Man hat festgestellt dass die Absorption des Kammerwassers und des Glaskörpers fast gleich der des Wassers ist wogegen die Absorption der Linse viel stärker ist und mit zunehmender Frequenz wächst (*Oksala* und *Lehtinen* 1958 *Nover* und *Glanschneider* 1965) In einer experimentellen Arbeit hat *Oksala* (1963) festgestellt dass bei einem Schallkopf von 6 MHz die Cornea und die Sclera eine im Vergleich zum Wasser geringe aber doch wahrnehmbare Ultraschallabsorption haben Bei einer andern experimentellen Untersuchung konnten *Oksala* und *Mela* (1964) mit einem Schallkopf von 6 MHz die Absorption der Sclera + der Chorioidea im Vergleich zum Wasser nicht ermitteln wohl aber mit einem Schallkopf von 18 MHz Zugleich nahmen sie wahr dass eine Änderung der Stellung der Augenhülle keine nennenswerten Veränderungen im Schallfeld hervorrief

In der vorliegenden Arbeit beabsichtigen wir mit einer neuen Apparatur

Diese Arbeit wurde von der Sigrid Juselius Stiftung unterstützt
Vorgetragen auf dem zweiten Kongress der SIDUO in Brno Mai 1967
Eingegangen am 9 September 1968

Tabelle 1

D e W rk ng de Lederha t bzw Hor hautkalotte auf d e B e t d s Schall bund ls

Die Ent ernung om Shall kopf bis zum M tallkugel	Die Richtung des chall strahles	D e Br ite des Shallbundels (mm)										
		Kontrollwerte	Messungen m t der Le derhautkalotte					Messu g m t de Hornhautkalotte				
			1	2	3	4	5	1	2	3	4	5
15 mm	92°	57±04	27	28	43	43	45	48	45	56	55	50
	91	58±01	30	35	52	49	46	50	49	60	53	56
	rt kal	56±03	26	45	50	43	44	45	50	58	60	58
	89°	53±04	30	36	40	47	48	46	51	53	52	55
	88	54±08	29	37	46	52	50	50	50	59	49	58
20 mm	92°	62±06	28	33	35	44	48	50	45	42	53	63
	91	61±07	29	43	39	58	44	50	50	52	50	40
	ert kal	59±08	32	35	46	44	40	43	46	45	50	42
	89°	59±09	36	39	37	41	50	45	46	45	44	40
	88°	59±05	38	42	41	48	49	48	46	52	49	43
25 mm	92°	60±09	38	35	34	40	50	47	46	43	44	39
	91°	60±08	32	38	45	44	41	48	43	49	43	47
	vert kal	61±09	37	38	40	46	41	49	42	47	40	49
	89°	59±06	39	35	39	40	45	50	51	44	45	43
	88°	60±08	39	35	40	42	42	50	50	46	42	48

auch mit den Ergebnissen die bei Untersuchung mit Hornhaut erhalten worden sind

Vergleichen wir dagegen die mit Lederhaut *und die mit Hornhaut erzielten* Resultate mit den Kontrollwerten so können wir feststellen dass beide Gewebe eine Verschmalerung des Schallbundels verursachen sowohl unter Beruck sichtigung der verschiedenen Entfernungen als auch der verschiedenen Winkel Obwohl die Verschmalerung nicht gross ist wird sie doch mit wenigen Aus nahmen aus der ganzen Tabelle ersichtlich Die von den Geweben verursachte Verschmalerung des Schallfeldes im Vergleich zu den Kontrollergebnissen nimmt mit wachsender Entfernung etwas zu Nur die Lederhauthullen 1 *und* 2 verursachen eine deutliche Verschmalerung aber die ubrigen Hullen sowohl von Lederhaut als auch von Hornhaut haben *eine untereinander* sehr ahnliche *geringe Wirkung In diesem* Zusammenhang haben wir Grund zu betonen dass die kleinsten Unterschiede in der Breite des Schallfeldes bei verschiedenen Mes sungen teilweise zufallsbedingt sind Das ruhrt daher dass das kleine Maximum am Rande des Schallfeldes *zuweilen klar hervortreten und zuweilen* wieder schwer *messbar sein kann*

Tabelle 2 zeigt den Einfluss der Lederhaut *und* der Hornhaut auf die Amplitude des hochsten Echos Die Messungsentfernungen und die *Richtungen* des Schallbundels sind dieselben wie in der *vorigen* Tabelle Die Kontrollmes

Die Untersuchungsweise

Der Zylinder, auf dem der Schallkopf fixiert wurde war so gebaut dass man ihn nach Wunsch mit einer Genauigkeit von 1° nach beiden Seiten drehen konnte Die Untersuchungen wurden zuerst mit kleinen Winkelunterschieden ausschliesslich in Wasser durchgefuhrt und zwar so dass die Kurven des relativen Schalldrucks gemessen wurden wenn der Schallkopf senkrecht stand d h in einem Winkel von 90°, und danach wenn er um 1° und 2° nach beiden Seiten gedreht war, also in fünf verschiedenen Stellungen Die Untersuchungs entfernungen vom Schallkopf zur Stahlkugel betrugen 15 20 und 25 mm Nach diesen Kontrollmessungen von denen in jeder Stellung fünf gemacht wurden wurde zwischen Schallkopf und Kugel zuerst die aus der Lederhaut bestehende und dann die aus der Hornhaut bestehende Hulle gelegt Dann wurden mit derselben Leistung der Maschine die entsprechenden Messungen vorgenommen Bei diesen wurden ausser der Breite des Schallfeldes und seiner Lage inbezug auf den Schallkopf auch die höchste Amplitude und ihre Lage berucksichtigt Als Untersuchungsobjekte dienten funf verschiedene aus Lederhaut bzw aus Hornhaut bestehende Hüllen

Zweitens wurde untersucht was für einen Einfluss ein grösserer schiefer Winkel auf die Kurven hat die den Schalldruck wiedergeben Die Kontroll messungen wurden wieder ausschliesslich in Wasser ausgefuhrt Wenn die Hulle hingesetzt worden war wurde das Schallbündel in einem Winkel von 15° gegen ihren Gipfel gerichtet Auf diese Weise wurden mit den oben genannten Entfernungen 2 Lederhaute und 2 Hornhaute untersucht

Die Ergebnisse

Tabelle 1 zeigt den Einfluss der Lederhaut und der Hornhaut auf die Breite des Schallbündels bei Untersuchung mit geringen Winkelunterschieden Man sieht in der Tabelle drei Untersuchungsentfernungen funf verschiedene Stel lungen des Schallkopfes die Kontrollresultate im Wasser sowie die Ergebnisse mit funf verschiedenen Leder- und Hornhauten Betrachtet man die Kontroll werte im Wasser so stellt man fest dass die Breite des Schallbündels bei den untersuchten Entfernungen und bei den funf verschiedenen Stellungen des Schallkopfes fast gleich bleibt Wenn wir die mit Lederhaut erhaltenen Mes sungsergebnisse betrachten lasst sich feststellen dass die Entfernungen und die verschiedenen Stellungen des Schallkopfes die Breite des Schallbundels nicht verandern die die ganze Zeit beinahe gleich bleibt und ebenso verhält es sich

Tabelle 1

D e W kung der Lederha t bzw Hor houtkalotte auf d e B e t e d s Schall bundels

D e Entfernung om Schall kopf bis zum M tollkugel	Die Richtung d s Schall strahles	D e B te des Shallbund ls (mm)										
		Kontrollwerte	M ssunge m t d r Le d houtkalotte					M ssunge m t de Ho nha t alotte				
			1	2	3	4	5	1	2	3	4	5
15 mm	92°	57±0.4	2.7	28	43	43	45	48	45	56	55	50
	91	58±01	30	35	52	49	46	50	49	60	53	56
	ert kal	56±03	26	45	50	43	44	45	50	58	60	58
	89°	53 04	30	36	40	47	48	46	51	53	52	55
	88	54±08	29	37	46	52	50	50	50	59	49	58
20 mm	92°	62 06	28	33	35	44	48	50	45	42	53	63
	91	61±07	29	43	39	58	44	50	50	52	50	40
	ert kal	59±08	32	35	46	44	40	43	46	45	50	42
	89°	5 09	36	39	37	41	50	45	46	45	44	40
	88°	59±05	38	42	41	48	49	48	46	52	49	43
25 mm	92°	60±09	38	35	34	4,0	50	47	46	43	44	39
	91	60±08	32	38	45	44	41	48	43	49	43	47
	vert kal	61±09	37	38	40	46	41	49	42	47	40	49
	89°	59±06	39	35	39	40	45	50	51	44	45	43
	88°	60±06	39	35	40	42	42	50	50	46	42	48

auch mit den Ergebnissen die bei Untersuchung mit Hornhaut erhalten worden sind

Vergleichen wir dagegen die mit Lederhaut und die mit Hornhaut erzielten Resultate mit den Kontrollwerten so konnen wir feststellen dass beide Gewebe eine Verschmalerung des Schallbundels verursachen sowohl unter Beruck sichtigung der verschiedenen Entfernungen als auch der verschiedenen Winkel Obwohl die Verschmalerung nicht gross ist wird sie doch mit wenigen Aus nahmen aus der ganzen Tabelle ersichtlich Die von den Geweben verursachte Verschmalerung des Schallfeldes im Vergleich zu den Kontrollergebnissen nimmt mit wachsender Entfernung etwas zu. Nur die Lederhautbullen 1 und 2 verursachen eine deutliche Verschmalerung aber die ubrigen Hullen sowohl von Lederhaut als auch von Hornhaut haben eine untereinander sehr ahnliche geringe Wirkung In diesem Zusammenhang haben wir Grund zu betonen dass die kleinsten Unterschiede in der Breite des Schallfeldes bei verschiedenen Mes sungen teilweise zufallsbedingt sind Das ruhrt daher dass das kleine Maximum am Rande des Schallfeldes zuweilen klar hervortreten und zuweilen wieder schwer messbar sein kann

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Die Untersuchungsweise

Der Zylinder auf dem der Schallkopf fixiert wurde war so gebaut dass man ihn nach Wunsch mit einer Genauigkeit von 1° nach beiden Seiten drehen konnte Die Untersuchungen wurden zuerst mit kleinen Winkelunterschieden ausschliesslich in Wasser durchgeführt, und zwar so dass die Kurven des relativen Schalldrucks gemessen wurden wenn der Schallkopf senkrecht stand d h in einem Winkel von 90° und danach wenn er um 1° und 2° nach beiden Seiten gedreht war, also in fünf verschiedenen Stellungen Die Untersuchungs entfernungen vom Schallkopf zur Stahlkugel betrugen 15 20 und 25 mm Nach diesen Kontrollmessungen von denen in jeder Stellung fünf gemacht wurden wurde zwischen Schallkopf und Kugel zuerst die aus der Lederhaut bestehende und dann die aus der Hornhaut bestehende Hulle gelegt Dann wurden mit derselben Leistung der Maschine die entsprechenden Messungen vorgenommen Bei diesen wurden ausser der Breite des Schallfeldes und seiner Lage inbezug auf den Schallkopf auch die hochste Amplitude und ihre Lage berucksichtigt Als Untersuchungsobjekte dienten funf verschiedene aus Lederhaut bzw aus Hornhaut bestehende Hüllen

Zweitens wurde untersucht was fur einen Einfluss ein grosserer schiefer Winkel auf die Kurven hat, die den Schalldruck wiedergeben Die Kontroll messungen wurden wieder ausschliesslich in Wasser ausgeführt Wenn die Hulle hingesetzt worden war, wurde das Schallbundel in einem Winkel von 15° gegen ihren Gipfel gerichtet Auf diese Weise wurden mit den oben genannten Entfernungen 2 Lederhaute und 2 Hornhäute untersucht

Die Ergebnisse

Tabelle 1 zeigt den Einfluss der Lederhaut und der Hornhaut auf die Breite des Schallbundels bei Untersuchung mit geringen Winkelunterschieden Man sieht in der Tabelle drei Untersuchungsentfernungen funf verschiedene Stel lungen des Schallkopfes die Kontrollresultate im Wasser sowie die Ergebnisse mit funf verschiedenen Leder und Hornhauten Betrachtet man die Kontroll werte im Wasser so stellt man fest dass die Breite des Schallbundels bei den untersuchten Entfernungen und bei den funf verschiedenen Stellungen des Schallkopfes fast gleich bleibt Wenn wir die mit Lederhaut erhaltenen Mes sungsergebnisse betrachten lasst sich feststellen dass die Entfernungen und die verschiedenen Stellungen des Schallkopfes die Breite des Schallbundels nicht verändern die die ganze Zeit beinahe gleich bleibt und ebenso verhalt es sich

Tabelle 1

D e W k ng der Lede ho t bzw Hornhautkalotte auf d e B e t e des Schall bundels

D e Entfernung om Shall kopf b s zum M tallkugel	D e Richtung des chall st ohles	D e B e te des Shallbundels (mm)										
		Kont allwerte	Messungen m t d r Le d hautkalotte					M ssu ge m t de Ho nhautkalotte				
			1	2	3	4	5	1	2	3	4	5
15 mm	92°	57±04	27	28	43	43	45	48	45	56	55	50
	91	58±01	30	35	52	49	46	50	49	60	53	56
	ert kal	56 03	26	45	50	43	44	45	50	58	60	58
	89°	53 04	30	36	40	47	48	46	51	53	52	55
	88	54±08	29	37	46	52	50	50	50	59	49	58
20 mm	92°	62±06	28	33	35	44	48	50	45	42	53	63
	91	61±07	29	43	39	58	44	50	50	52	50	40
	vert kal	59±08	37	35	46	44	40	43	46	45	50	42
	89°	59±09	36	39	37	41	50	45	46	45	44	40
	88°	59±05	38	42	41	48	49	48	46	52	49	43
25 mm	92°	60±09	38	35	34	40	50	47	46	43	44	39
	91	60±08	32	38	45	44	41	48	43	49	43	47
	ert kal	61±09	37	38	40	46	41	49	42	47	40	49
	89°	59±06	39	35	39	40	45	50	51	44	45	43
	88°	60±08	39	35	40	42	42	50	50	46	42	48

auch mit den Ergebnissen, die bei Untersuchung mit Hornhaut erhalten worden sind

Vergleichen wir dagegen die mit Lederhaut und die mit Hornhaut erzielten Resultate mit den Kontrollwerten so können wir feststellen dass beide Gewebe *eine Verschmalerung* des Schallbundels verursachen sowohl unter Berucksichtigung der verschiedenen Entfernungen als auch der verschiedenen Winkel Obwohl die Verschmalerung nicht gross ist wird sie doch mit wenigen Ausnahmen aus der ganzen Tabelle ersichtlich Die von den Geweben verursachte Verschmalerung des Schallfeldes im Vergleich zu den Kontrollergebnissen nimmt mit wachsender Entfernung etwas zu Nur die Lederhauthullen 1 und 2 verursachen eine deutliche Verschmalerung aber die ubrigen Hullen sowohl von Lederhaut als auch von Hornhaut haben eine untereinander sehr ahnliche geringe Wirkung In diesem Zusammenhang haben wir Grund zu betonen dass die kleinsten Unterschiede in der Breite des Schallfeldes bei verschiedenen Messungen teilweise zufallsbedingt sind Das ruhrt daher dass das kleine Maximum am Rande des Schallfeldes zuweilen klar hervortreten und zuweilen wieder schwer messbar sein kann

Tabelle 2 zeigt den Einfluss der Lederhaut und der Hornhaut auf die Amplitude des hochsten Echos Die Messungsentfernungen und die Richtungen des Schallbundels sind dieselben wie in der vorigen Tabelle Die Kontrollmes

Tabelle 2

Die Wirkung der Lederhaut – bzw Hornhautkalotte auf die Hohe des Amplituden maximus

Die Entfernung vom Schall kopf bis zum Metallkugel	Die Richtung des Schall strahles	Die hochsten Amplituden										
		Kontrollwerte	Messungen mit der Lederhautkalotte					Messungen mit der Hornhautkalotte				
			1	2	3	4	5	1	2	3	4	5
15 mm	92°	14 8 ± 0 4	12	9	12	11	13	13	13	14	11	13
	91°	15 0 ± 0 0	9	12	12	11	14	13	13	14	12	13
	vertikal	15 0 ± 0 0	10	13	13	11	14	13	13	14	12	12
	89°	14 6 ± 0 5	11	14	14	11	14	14	14	14	13	12
	88°	15 0 + 0 0	11	13	13	11	14	14	14	14	12	13
20 mm	92°	13 4 ± 0 9	7	8	11	10	11	12	11	13	12	10
	91°	13 6 ± 0 5	7	11	10	10	13	12	12	13	12	11
	vertikal	13 8 ± 0 4	8	12	12	10	13	13	12	13	12	11
	89	13 4 ± 0 5	10	12	12	11	13	12	12	13	11	12
	88°	13 8 ± 0 4	9	11	12	11	12	12	13	13	12	12
25 mm	92°	12 8 ± 0 4	6	6	10	10	10	11	11	12	10	8
	91°	13 0 ± 0 0	6	11	9	10	11	11	11	12	12	9
	vertikal	12 8 ± 0 4	7	11	11	10	12	11	11	12	12	9
	89°	12 8 ± 0 4	8	11	12	10	12	11	11	10	10	10
	88	12 8 ± 0 4	7	9	12	10	12	11	10	12	10	10

sungen wurden wieder im Wasser vorgenommen Wenn man die Kontrollwerte bei den drei verschiedenen Entfernungen betrachtet bemerkt man dass eine kleine Veränderung des Einfallswinkels des Schallbündels nicht nennenswert auf die Hohe der Amplitude einwirkt Vergleicht man dagegen die bei verschiedenen Entfernungen erhaltenen Ergebnisse so stellt man fest dass die hochste Amplitude mit wachsender Entfernung in der Regel etwas kleiner wird Wenn man die Zahlen prüft die mit Lederhauthüllen und mit Hornhauthullen erhalten worden sind kann man dieselbe Beobachtung machen d h die Veränderung der Stellung des Schallkopfes hinsichtlich der Hulle beeinflusst die Amplitude nicht aber bei zunehmender Entfernung wird das höchste Echo ein wenig niedriger Beim Vergleich zwischen dem Einfluss der Lederhaut und dem der Hornhaut lässt sich feststellen das beide ein geringes Niedrigerwerden des höchsten Echos verursachen und dass die Lederhaut diese Wirkung stärker ausubt als die Hornhaut

Abb 1 zeigt die mit einer Lederhaut und einer Hornhaut erzielten Ergebnisse nun aber durch Zeichnungen veranschaulicht Daraus geht erstens hervor dass bei einem um 1° oder 2° schiefen Auftreffen des Schallbündels auf die Lederhaut oder Hornhaut keinerlei Brechung des Schallbundels bei den untersuchten Entfernungen geschieht Zweitens wird in der Abbildung anschaulich sichtbar dass die Lederhaut und die Hornhaut sowohl eine geringe Verschmalerung des Schallfeldes als auch ein Niedrigerwerden der Maxima der den Schalldruck

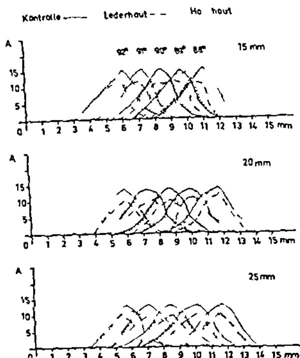


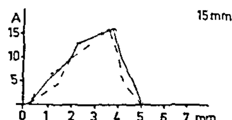
Abb 1

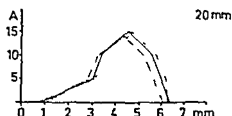
Der Einfluss der Lederhaut und Hornhaut auf die relativen Echoamplitudekurven untersucht in verschiedenen Richtungen des Schallstrahles und in drei Entfernungen

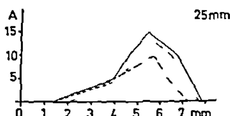
darstellenden Kurven verursachen Beide Gewebe absorbieren mehr Ultraschall als das Wasser die Lederhaut aber etwas mehr als die Hornhaut Wenn man das Schallbundel in einem Winkel von 15 gegen den Gipfel der Hulle richtete wurden mit zwei Lederhauthullen und zwei Hornhauthullen sehr ahnliche Ergebnisse erzielt Abb 2 zeigt die mit einer Lederhaut und einer Hornhaut erhaltenen Druckkurven im Vergleich zu den Kontrollmessungen Auch jetzt verursachen die untersuchten Gewebe keine Brechung des Schallbundels Die Absorption der Gewebe tritt am besten bei einer Entfernung von 25 *mm* zutage und die Absorptionsunterschiede entsprechen den obenerwahnten

Besprechung

Bei den Kontrolluntersuchungen im Wasser wurde festgestellt dass die Breite des Schallfeldes bei den Untersuchungsentfernungen 15 20 und 25 mm nahezu







Kontrolle —— Lederhaut- - - Hornhaut

Abb 2

Der Einfluss der Lederhaut und Hornhaut auf die relativen Echoamplitudekurven untersucht mit einem Winkel von 15° des Schallkopfes und in drei Entfernungen

gleich war, auch in den Fällen wo die Stellung des Schallkopfes vom senkrech ten Winkel von 90° um 1° und 2° nach beiden Seiten schwankte Die Lederhaut und die Hornhaut verursachten im Vergleich zum Wasser nur eine geringe Verschmälerung des Schallfeldes und zwar war diese bei der Lederhaut ein wenig grösser

Die Amplitude des hochsten Echos sank bei allen Messungen mit wachsender Entfernung Hingegen hatten Veranderungen der Stellung des Schallkopfes keinen Einfluss auf die Amplitude Die Lederhaut verursachte ein etwas stärkeres Absinken der Amplitude als die Hornhaut Eine geringe Veranderung der Richtung des Schallbundels gegenuber der Senkrechten d h 90° um 1° und 2° nach beiden Seiten führte bei den untersuchten Entfernungen zu keiner Verschiebung der Schallfelder und der Echomaxima im Vergleich zu

den Kontrollmessungen Bei Untersuchung mit einem grösseren schiefen Winkel d h einer Abweichung um 15° war das Ergebnis dasselbe Daraus kann man den Schluss ziehen dass das Schallbundel nicht gebrochen wird wenn es in den angewandten Winkel schief auf die Lederhaut oder auf die Hornhaut auftrifft

Betrachtet man die mit verschiedenen Lederhauten und verschiedenen Hornhauten erhaltenen Messungsergebnisse so bemerkt man dass die mit den Hornhauten erzielten Werte einander naherliegen Das durfte herruhren dass die Lederhauthullen in ihren Eigenschaften hauptsachlich in ihrer Dicke nicht ebensosehr einander ahnlich sein konnten wie die Hornhauthullen Solche Lederhauthullen die man von weiter hinten genommen hatte hatten wahrscheinlich eine noch grossere Absorption gehabt Obwohl die Zahl der Messungen nicht sehr gross ist sprechen sie doch alle fur die obigen Schlussfolgerungen

Im Hinblick auf die klinische Diagnostik hat die Erkenntnis dass das Schallbundel in der Lederhaut nicht gebrochen wird eine grosse klinische Bedeutung vor allem fur die Lokalisation pathologischer Zustande Die geringe Absorption der Lederhaut und der Hornhaut kann nur die Diagnostik sehr schwacher Glaskorpertrubungen erschweren

Bei biometrischen Messungen durch die Lederhaut hindurch verursacht nach dieser Untersuchung eine geringe Richtungsanderung des Schallbundels nicht den Fehler der bei axialen Messungen infolge der von der Linse verursachten Brechung entsteht

Die Absorption der Lederhaut und der Hornhaut hat dagegen keinen Einfluss auf biometrische Messungen

Zusammenfassung

Mit Hilfe von Schweineaugen wurde der Einfluss der Lederhaut und de Hornhaut auf das Schallfeld im Vergleich zu Wasser experimentell untersucht Die Untersuchungsergebnisse haben erwiesen dass die Lederhaut und die Hornhaut das Schallfeld ein wenig verschmalern und zwar die Lederhaut etwas mehr als die Hornhaut Mit wachsender Untersuchungsentfernung sinkt die hochste Amplitude ein wenig sowohl die Lederhaut als auch die Hornhaut lassen diese Amplitude etwas niedriger werden wobei wieder der Einfluss der Lederhaut starker ist als der der Hornhaut Die Lederhaut und die Hornhaut verursachen keine Brechung des Schallbundels obwohl dieses schrag (1° 2 und 15) durch sie hindurchgeht

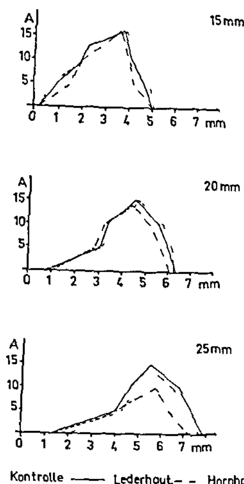


Abb 2

Der Einfluss der Lederhaut und Hornhaut auf die relativen Echoamplitudekurven untersucht mit einem Winkel von 15° des Schallkopfes und in drei Entfernungen

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From the Ophthalmic Pathology Laboratory
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(Head S Ry Andersen)

TERATOMA OF THE ORBIT

BY

O A JENSEN

Teratoma of the orbit is rather rare The published number of cases is about 40 They all had a uniform clinical picture and were very similar in their morphological pattern often polycystic and with various amounts of solid tissue

The present case is of particular interest because it showed highly differentiated neuroectodermal structures interpreted as *ocular primordia* The detailed clinical and therapeutical aspects of the case are published elsewhere [1]

Case Report

Clinical history (Sahlgrenska sjukhuset Gothenburg *rec. no* 8[illegible]720) A new born girl presented with a large tumour of the *right orbital* region. The parents were healthy The mother was [illegible] *years old* and had had one normal delivery two years previously This child was healthy The estimated length of the pregnancy was 3[illegible] weeks There was no infectious disease no X ray exposure and no drug consumption during the pregnancy

The delivery was normal The birth weight was [illegible] g the length 45 cm the circumference of the head 3[illegible] cm This corresponds to a prematurity of three weeks

Examination The baby was healthy and without malformation apart from a big hemispherical tumour *protruding* from the right orbital region (*Fig 1*) The diameter

Read in an abbreviated form before the European Ophthalmic Pathology Society Paris 16–19th May 19[illegible]

Received September 13th 19[illegible]

Nover A und *Glanscl neider D* Untersuchungen uber die Fortpflanzungsgeschwindigkeit und Absorption des Ultraschalls im Gewebe Graefes Arch Ophthal *168* 304–321 (1965)

Oksala A Experimental and clinical observations on the echograms in vitreous haemorrhagia Brit J Ophthal *47* 65–70 (1963)

Oksala A and *Lehtinen A* Absorption of ultrasound in the aqueous humour lens and vitreous body Acta ophthal Kbh *36* 761–768 (1958)

Oksala A and *Mela M J* Experimental researches on the significance of the interference phenomenon with the near field in diagnosis of the eye by ultrasound particularly with regard to search for a foreign body Acta ophthal Kbh *42* 179–187 (1964)









Fig 6

Cartilage with incipient bone formation (× 35)

Fig 7

Intestinal lumen. Note the circular and longitudinal muscles (× 35)

Fig 8

Skin surface (× 35)

Fig 9

Nervous tissue. Granular tissue with rosettes (× 90)





Fig 4
Cystic and solid areas of the sectioned orbital tumour
Fig 5
Survey of one of the histological sections The black areas are cartilage and bone A skin surface can be seen in the upper right corner (× 1 5)

columnar epithelium often with mucous secretion Several of these lumina were surrounded by circularly and longitudinally oriented smooth muscle (Fig 7) In some sections glandular tissue in connection with these lumina were found probably pancreatic tissue although no islets were identified Some lumina had the character of endometrial cysts









Fig 6
Cartilage with incipient bone formation (× 35)
Fig
Intestinal lumen. Note the circular and longitudinal *muscles* (× 55)
Fig 8
Skin surface (× 35)
Fig 9
Nervous tissue. Granular tissue with *rosettes* (× 90)

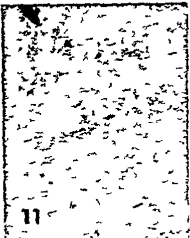




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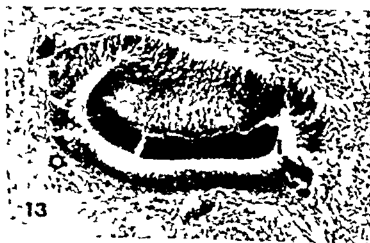


Fig 10

Cl s up f pen lym l ro ette The lim it ng membrane can be clearly seen (X 245)

Fig 11

Nerv us tissue similar to white matter of the cerebrum (X 35)

Fig 1

Gangl n Peripheral nerv us tissue can be seen to th e right (X 3)

Fig 13

Opt cup format on I Inner layer of the cup with embryonal retinal inner layer O Outer layer of the cup with pigmented epithel um A rosette can be seen (arrow) (X 60)

Ectodermal components were found in the form of skin with hair (Fig 8) and sebaceous glands several dermoid cysts and sweat glands and ducts

Neuroectodermal tissue constituted a large part of the tumour Both differentiated and undifferentiated nervous tissue was seen The latter was observed as a granular tissue similar to Obersteiner s granular subpial layer present throughout the cerebellar cortex at birth The origin of medulloblastomas is postulated from this layer Scattered in these areas were ependymal diktyoma like rosettes (Fig 9) The cells forming the rosettes were uniform with some mitoses (Fig 10) The internal limiting membranes of the rosettes were not coloured by PAS Alcian blue or Colloidal iron stains and the cytoplasm of the rosette forming cells was not stained by Cresyl echt violet Tissue resembling white matter of the cerebrum was found in other areas (Fig 11) Several ganglia (Fig 12) and peripheral nervous tissue were present as well as cavities with choroid plexus

Bodian and PTAH stain revealed nervous fibres in and around the ganglia

The most interesting finding was small fields with brownish black pigmented tissue The pigment was bleached by potassium permanganate and stained black by the Masson Fontana process but was not stained by Prussian blue A linear band of cells resembling the inner layer of the foetal retina was often found and in a few sections both layers were bent forming an optic cup (Fig 13) often peripherally placed simulating laterally located cups

Discussion

In my opinion only a tumour derived from all three germinal layers should be called a teratoma If the tumour is composed of tissue from only two germinal layers (the endodermal components most often being absent) it should be termed teratoid Tumours with tissue from only one germinal layer in the orbit i e dermoid cysts and epidermal cysts are choristomas The only teratomas consisting of only one kind of tissue are those rare highly malignant tumours composed of undifferentiated embryonic tissue[3]

Tumours of the kind presented in this publication are confined to the orbit but may of course if not removed in time impress themselves on surrounding structures

The orbit may be invaded or even filled by a part of a larger teratoma from the base of the brain or from the maxilla but such tumours are probably not primarily orbital Such a case was presented by *Hanssens*[4] at the 7th Meeting of the European Ophthalmic Pathology Society 1968

The number of orbital teratomas of the same kind as the one here reported

According to Willis[18] malignancy in teratomas may be of the following three kinds a) total malignancy of embryonic teratomas b) malignancy of one component only of a previously benign teratoma most often squamous cell *carcinoma* of the skin or c) peritoneal dissemination of relatively benign teratomatous tissues

The present teratoma belongs to none of these categories I consider it to be a benign growth in spite of the undifferentiated nervous tissue and in spite of Willis statement[18] that malignant growths contain all degrees of immaturity of nervous tissue particularly neuroepithelial tubules and plaques This of course is a matter of definition If Willis means only active growth with expansion in the orbit I agree In point of fact an increase in size of the present tumour was observed but it does not fulfil the characteristics of the common malignancy concept it is not a teratocarcinoma

The ependymal rosettes in the undifferentiated nervous tissue are similar to the rosettes of diktyomas According to *Ry Andersen*[17] 75 % of all diktyomas are benign even if a tendency to active growth is common This is reasonably in accordance with the considerations above

Ocular tissue has been found in some instances in ovarial[18, 19, 20] testicular [20, 21] coccygeal[20] hypophyseal[22] and in an intracranial teratoma[23] The latter case of *Denes*[23] was perhaps an orbital teratoma with its largest mass of tissue in the anterior half of the cranial cavity But otherwise ocular tissue has not been found in orbital teratomas In all these cases only the *pigmented outer* layer of the retina has been found but no retina *proper as in* the present case where the layer of cells internal to the pigmented layer in some areas had a morphology similar to the embryonal inner layer of the retina

We have recently had an opportunity to see a large maxillo orbital teratoma with ocular tissue A small area in one lumen had a structure like the embryonal inner layer of the retina[24]

Summary

A healthy new born baby presented with a large protruding tumour located solely in the orbit The tumour was *sucessfully extirpated* The tumour was macroscopically composed of cystic and solid areas and microscopically it was seen to be a benign teratoma with differentiated and more undifferentiated tissue from all three germinal layers It *contained a large* amount of nervous tissue with ependymal rosettes and as a unique *feature* ocular primordia with tissue from both the outer and inner layers of the optic cup

were found by *Hoyt and Joe*[5] to be 30 Including their case the published number up to the present time has increased to 39 the present case excluded[4 1] Histopathological examination has been carried out in 32 of these cases

Regarding the histogenesis of teratomas various hypotheses have been proposed but no agreement has been reached A good survey of these hypotheses can be found in *Hoyt and Joe s* publication[5] as well in those of *Nicholson*[13] and of *Willis*[3 14 15]

Although the popular hypothesis that a teratoma represents a distorted fetus is not supported by several authors a foetoid structure may be observed in several teratomas This is also seen in the present case (Fig 14) The drawing is based on an addition of serial sections

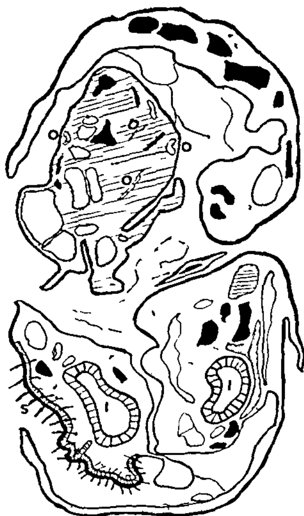


Fig 14

Sketch of the tumour based on serial sections to demonstrate foetoid structure Black Cartilage and bone Stippling Mesodermal tissue Hatching Nervous tissue I Intenstinal lumina O Ocular structures S Skin surface

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Acknowledgement

The author is indebted to the doctors of the Department of Plastic Surgery and the Department of Ophthalmology, Sahlgrenska Sjukhuset Gothenburg for referring the specimen and for the permission to publish this case from a histopathological aspect

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I Pearl tumours in the iris
II Post traumatic cysts in the iris
III Epithelization of the anterior chamber

Group I and II concern implantation cysts originating by implantation of epithelial cells of a hair follicle perhaps in connection with a cilia or from implanted skin Group III concerns epithelial invasion from cornea or conjunctiva through a perforating lesion of cornea or sclera following either accident or operation

The etiology the clinical picture the treatment as well as the histopathological and experimental examinations have been discussed in various papers[10-23]

The aim of the present work is a clinical and histopathological estimation of epithelization of the anterior chamber during a period of 25 years based on a Danish histopathological material consisting of enucleated eyes (The Ophthalmic Pathology Laboratory receives abt 95 per cent of all enucleated eyes in Denmark)

Material

In the files of The Ophthalmic Pathology Laboratory from 1943–67 33 cases were found with epithelization of the anterior chamber i e a little more than one case per annum Of these 16 cases had originated from accidental perforations (12 right sided and 4 left sided) and 1 cases had originated from intraocular operations (7 were right sided and 10 left sided)

Fig 1 shows the sex and age distribution in the material at the time of injury

As regards the cases of perforation their frequency was highest among children and adolescents which is easily explained by the fact that perforations occur most often in this age group[24]

Due to operations incidence of epithelization was highest in the older age group which corresponds to the greater frequency of cataract extractions in this group

Epithelization of the anterior chamber following accidental perforations and intraocular operations will be discussed separately

I Epithelization of the Anterior Chamber following accidental perforations

In 12 cases the perforations were in the cornea in 2 in the sclera and in 2 the location was corneo scleral In 11 cases there was prolapse of the uveal tissue

Of the above 16 cases 14 were sutured (Table I)

From The Ophthalmic Pathology Laboratory
University of Copenhagen Denmark
(Head S Ry Andersen)

EPITHELIZATION OF THE ANTERIOR CHAMBER

A Clinical and Histopathological Study of a Danish Material

BY

P ELDRUP-JORGENSEN

For over a century epithelial growth in the anterior chamber has been of interest to ophthalmologists

As early as in 1835 McKenzie[1] described a semi translucent cyst in the anterior chamber after a perforating injury

In 1872 Rothmund published a clinical study of epithelial cysts in the anterior chamber and in the iris

From his investigations Rothmund concluded that these cysts originated from the implantation of epithelium in the anterior chamber following perforating lesions

In 1873 this theory was opposed by von Wecker[3] who thought that the cysts originated when the surface of the iris was folded or iris tissue adhered over a crypt

However the experimental tests of Masse[4] and others[5,6] as well as the histopathological studies of Collins and Cross[7] Guaita[8] and Meller[9] soon confirmed Rothmund s theory

Our knowledge of the etiology has since increased considerably

In 1937 Perera[10] was able to differentiate between three types of epithelial invasion of the anterior chamber

Received September 19th 1968
Read in an abbreviated form at the 417th Session of the Danish Ophthalmological Society Nyborg Strand 4th to 5th May 1968

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Fig 1

Table 1
Surgical Treatment of Accidental Perforations

Corneal suture	4
Scleral suture	1
Conjunctival flap	2
Corneal suture + conjunctival flap	2
Scleral suture + conjunctival flap	1
No suture	2
No information	4

Information on the suturing material was scarce The diagnosis – epithelization of the anterior chamber – was established clinically in 10 of these 16 cases (abt 63 per cent) Out of these 8 were described as cystic of which 5 were

situated on the surface of the iris and 3 free of the iris One case was found to be non cystic and one was described as a pearl tumour

Table 2 shows the interval between the injury and the clinical establishment of epithelization The shortest interval was 13 weeks the longest 52 years

In 4 of the 10 clinically established cases treatment was attempted The Pearl tumour was removed by broad iridectomy Two iris cysts were extirpated and in one case a puncture was performed

As for the pearl tumour the treatment led to good results with function maintained In the remaining three cases the eyeballs were later enucleated or eviscerated Thus the final result was that in 15 of the 16 cases enucleation or evisceration had been performed

The time from injury to enucleation or evisceration is shown in Table 3 The shortest interval was 14 days the longset 60 years

The main indications for enucleation or evisceration can be seen from Table 4 showing that glaucoma inflammation and fear of sympathetic ophthalmia were among the most frequent causes This is in contrast to the other group comprising the operations mentioned below in which glaucoma was by far the most frequent cause

Histopathological Examinations

For the microscopic examination Perera s grouping (see above) is used

Thus we found One case of pearl tumour foud iris cysts and eleven cases with epithelization No distinction was made between cystic and non cystic invasion

Table 2

Time Elapsed between Trauma and Clinical Establishment of Epithelian *Invasion* after Accidental Perforations

0–6 mths	0
6–1 mths	1
1–3 years	3
3–6 years	1
18 years later	1
5 years later	1
No information	1
Total	10

Table 3
Time Elapsed between Trauma and Enucleation/Exenteration after Accidental Perforations

0 – 2 weeks	1
2 – 4 weeks	1
1 – 3 mths	1
3 – 6 mths	1
6 – 12 mths	1
1 – 2 years	2
2 – 3 years	1
3 – 6 years	1
6 – 12 years	2
12 – 18 years	3
60 years later	1
Total	15

Table 4
Main Indications for Enucleation/Exenteration

Glaucoma	4
Glaucomatous iridocyclitis	2
Inflammation	4
Sympathetic ophthalmitis possible	5
Haemophthalmos	1

The associated histopathological changes can be seen from Table 5

The case of sympathetic ophthalmia was not established clinically nor was it therefore in the five cases where the bulbi were removed for fear of this complication

II Epithelization of the Anterior Chamber following Intraocular Operations

This group which is rather more interesting comprises cases where intra ocular operations were performed owing to disease of the eye and where the micro scopy revealed epithelization of the anterior chamber

Table 5
Associated Histopathological Changes after Accidental Perforations

Glaucoma (secondary)	2
Cataract (secondary and traumatic)	1
Iridocyclitis	9
Panophthalmitis	1
Haemophthalmos	4
Detachment of the retina	1
Sympathetic ophthalmitis	

Seventeen cases were found in all The age and sex distribution are mentioned in the introduction

Table 6 shows the number and type of operations performed

The records show that four were intracapsular cataract extractions while twelve were extracapsular of which five were intended intracapsularly

Iridectomy was performed in ten extracapsular and in three intracapsular cases There were no complications during operation in two of the extracapsular and two of the intracapsular cases

Table 7 shows the complications that occurred in the remaining 13 cases

The figures must be regarded as minimum and it should be noted that the most frequent complication was rupture of the crystalline capsule

The postoperative complications are shown in Table 8

Epithelization of the anterior chamber was clinically established in 11 of the above 17 cases i e abt 65 per cent with a frequency similar to that of the perforations

Table 6
Operations

Cataract extraction	
extracapsular incl cases of subsequent discission	12
intracapsular	4
Glaucoma surgery	1
Total	17

Table 7
Complications after Surgical Treatment

	Extracapsular	Intracapsular
Rupture of lens capsule	5	
Uveal protrusion	1	
Protrusion of vitreous	2	
Heavy haemorrhage		1
Synechias	2	1
Difficulties by suturing	1	
	11	2

Table 8
Postoperative Complications after Surgical Treatment

	Extracapsular	Intracapsular
Wound rupture	2	
Prolapse or incarceration of iris	4	
Flat chamber		2
Severe inflammation		1
Herniation of vitreous	1	
Severe corneal oedema	3	

Of the 11 cases 4 were described as cystic 2 as iris cysts and 2 without any relation to the iris In the remaining 7 a greyish film was found on the posterior surface of the cornea

It is impossible to give any interval between operation and clinical establishment of epithelization as various operations had been performed in the same eye in several cases and it cannot be determined which operation resulted in epithelization

Only in 2 of the cases was treatment of the epithelization attempted One case involved extirpation of a cyst free of the iris At follow up 7 years later there were no signs of recurrence of epithelization However there was slightly

increased tension The other case concerning a non cystic invasion was treated with X rays without effect however

In the remaining 15 cases the bulbi were removed without preceding therapy

It is surprising that X ray treatment was not used more often especially as it was a question of aphacic eyes The main indication for the removal of the eyes can be seen in Table 9 which reveals that glaucoma was by far the most frequent cause

Histopathological Examinations

Microscopy showed epithelial invasion to be present in 16 cases and iris cyst in one The associated pathological changes are listed in Table 10

Discussion

In order to obtain an impression of how frequently epithelization of the anterior chamber is a complication of cataract extractions resulting in removal

Table 9
Main Indication for Enucleation Exenteration after Surgical Treatment

Sec glaucoma	12
Haemophthalmos	1
Sympathetic ophthalmitis possible	1
Phthisis	1

Table 10
Associated Histopathological Changes after Surgical Treatment

Glaucoma	10
Sec cataract	10
Iridocyclitis	8
Sympathetic ophthalmitis possible	1
Prolapse or incarceration of iris	5

of the eye the author totalled the number of eyes received at The Ophthalmic Pathology Laboratory during the above mentioned 25 year period when cataract extractions had been performed The number amounted to 19? of which 16 showed epithelization of the anterior chamber (abt 8 per cent)

Similar results of investigations in other departments can be seen in Table 11

The reason why the percentage may be lower in Denmark compared with other countries may be the fact that the collection of cases covers recent years and also that epithelization may have grown more rare However this is not the case as the following evidence shows During the first half of the period 93 eyes enucleated after cataract operations were received of which 5 showed epithelization In the second half of the period 99 eyes were received 11 with epithelization Expressed in percentages this means 5 4 and 11 1 per cent respectively which is more than a doubling in the second half of the period

This might be due to a change in operative technique suture material and operative skill during the latter period Information from the recorded material is however, insufficient for any true estimate to be made

The patient material itself has undergone certain changes as indications for treatment of cataract extraction have been extended recently in Denmark so that a larger number as well as more complicated cases are operated upon Further the patients are in a higher age group than previously Thus in our material of postoperative epithelization in the last period there was one patient with diabetes mellitus but none in first period Furthermore the average age in the last period was 68 against 50 in the first

In about 75 per cent of the material complications arose during the cat

Table 11

Eyes Enucleated after Cataract Extraction (after Maumenee A L Trans Am Acad Ophth and Otol 61 Page 52 19?7) Including own Figures

Institution	No Eyes Removed	No with Epithel	%	Dates
Inst of Ophth Presb Hosp N Y	35	4	11	19?9-35
Illinois Eye and Ear Infir	75	14	18	1934-45
Univ of Iowa	145	30	20	
Standford Univ	4?	9	21	1949-55
Armed F Inst of Path	889	113	12	1944-53
Ophth Path Lab Univ Copenhagen	192	16	8	1943-67
Total	*1379*	*186*	13 5	

aract operations and might have been the cause of delayed healing which increases the risk of epithelization considerably

Badly matched wound edges sutures placed too deeply incarceration of remnants of crystalline capsules vitreous iris and conjunctiva or foreign bodies will cause delayed healing of wounds Generalized disease and old age also predispose towards the delayed healing of wounds

Thus there are various possible causes for the doubling of epithelization following cataract extractions in the latter half of the period but the material offered no clarification of these

Summary

In a Danish material from The Ophthalmic Pathology Laboratory from 1943 67 33 cases were found with epithelization of the anterior chamber 16 cases following accidental perforations 17 following intraocular operations

The material was divided into these two groups and the clinical and histopathological findings were assessed

As regards the accidental perforations the main indications for the removal of the eyes were equally divided between glaucoma inflammation and fear of sympathetic ophthalmia However glaucoma was by far the main cause in the case of the operations

Implantation cysts constituted about 30 per cent of the epithelization of the anterior chamber in accidental perforations but only 6 per cent in the operations

In the above mentioned 25 year period 192 eyes were received after previous cataract extractions Of these about 8 per cent had epithelization of the anterior chamber Twice as many cases occurred in the second period compared with the first

Epithelization of the anterior chamber is still a serious complication following perforations whether accidental or due to intraocular operation Furthermore the investigation seems to indicate that this complication occurs more often after cataract extractions The causes for this are discussed

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UNSERE ERFAHRUNGEN ÜBER DIE RÖNTGENSTRAHLEN-BEHANDLUNG BEI ENTZÜNDLICHEN AUGENERKRANKUNGEN DES VORDEREN BULBUSSEGMENTES

VON

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Einführung

Die klinische Anwendung der Röntgennah-Bestrahlung stellt ein seit 1942 *(Colombo)* bei den entzündlichen Erkrankungen des Auges bekanntes therapeutisches Verfahren dar. Es erwies sich zwar als brauchbar, wird aber noch immer nicht allgemein angewandt, da seine Methodik und Dosierung noch nicht einheitlich sind, ein Umstand, der vielleicht auf die Furcht vor den verschiedenen Gewebeschädigungen zurückzuführen ist. Hand in Hand mit der Entwicklung der Bestrahlungstechnik (genaue Dosierung, Anwendung der Röntgenstrahlen in entsprechenden Tiefen, Strahlenschutz) wird es immer evidenter, dass diese Furcht im Grunde unbegründet ist.

Wir selbst haben die Röntgenbestrahlung (Plesio-Therapie) vor nahezu 3 Jahren eingesetzt. Es zeigte sich, dass dieses Verfahren immer bei hartnäckigen entzündlichen und häufig rezidivierenden Fällen indiziert war, die sich bei konservativer Behandlung durchaus nicht besserten. Zur Behandlung des

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1 Dakryocystitis subacuta

In allen drei Fallen fand sich in der Anamnese eine seit Jahren bestehende Dakryocystitis die zeitweise mit heftigen Symptomen einherging (Schmerzen Schwellung Rotung usw) In dieser Phase pflegten wir den erkrankten Tranensack dreitagig mit einer *Dosis* von *50 r* (*insgesamt 200 r*) *zu bestrahlen* (50 kV 20 mA Al F 1 mm FHA 15 cm) wobei eine Tube von 2 cm Durchmesser benutzt wurde

Nach dieser Behandlung bildete sich die Entzundung bei allen drei Patienten in wenigen Tagen fast ganzlich zuruck und auch die *Schmerzen* klangen allmahlich ab Wahrend der Dauer der Strahlentherapie *wurden den Patienten* keinerlei Arzneimittel verabreicht

2. Blepharitis chronica

In unseren 5 Fallen mit bilateralen Blepharitis die seit 2–15 Jahren bestanden und auf verschiedene Lokalbehandlungen nicht angesprochen hatten, wurde zweitagig eine Dosis von 30–50 r (insgesamt 250 r) gegeben (30 kV 20 mA, Al F 0 3 FHA 15 cm) In zwei Fallen bei denen die Krankheit schon seit 10 bzw 3 Jahren dauerte klangen Lidrotung und Schuppung zwei Wochen nach der Behandlung ganz ab ohne zu rezidivieren (Dauer der Beobachtung 6 Monate!) Bei den ubrigen drei Patienten schwanden die Symptome einige *Wochen nach* der Strahlenbehandlung Bei der Kontrolluntersuchung berichteten die *letztgenannten* Personen dass sie wahrend dieser Zeit hin und wieder einen Ruckfall allerdings mit *weniger heftigen* Symptomen als bevor der Rontgenbestrahlung beobachtet hatten

3 Keratitis superficialis

a Keratitis herpetiformis 4 Falle

b Caustio corneae (Ulcus corn) 3 Falle

Sowohl den Herpes – als *auch* den Ulkus – Kranken wurden *3* bis 4 tagig 30–50 r gegeben (10 kV 20 mA F 0 FHA 15 cm) Bei den Herpes Kranken betrug die Gesamtdosis 150 r bei den Ca Geschadigten 200–500 r Die Herpes *Kranken zeigten keinerlei Besserung* bei den anderen setzten die Epithelisation der *Kornea und das* Abklingen der Trubung binnen einer Woche ein

4 Leukoma und Vaskularisation der Hornhaut

Den sieben Patienten unseres Krankengutes wurden 2tagig 50–80 r gegeben (10 kV 20 mA F 0 FHA 15 *cm*) In 2 Fallen betrug die Gesamtdosis nur 250 r in den ubrigen (5) 400–500 r (Bei niedrigeren Gesamtdosen liessen sich keine Ergebnisse erzielen) Bei *diesen* 5 Fallen gelang es eine weitere Vasku

vorderen Bulbussegmentes ist die Plesio Therapie wegen ihres Oberflächeneffektes und ihrer Komplikationslosigkeit geradezu prädestiniert

Methodik

In unserem Institut werden die Bestrahlungen mit Hilfe eines in der DDR hergestellten TUR T 60 Gerätes bei einer Stromstärke von 20 mA vorgenommen Je nach der Tiefe der zu bestrahlenden Gewebe gelangen Spannungen von 10 30 40 und 50 kV und in Abhängigkeit von der jeweiligen Spannung Al Filter mit einer Dicke von 0 0 3 0 6 und 1 0 mm zur Anwendung Eine 15 cm lange Bleiglastube (Fokus Hautabstand) von 1 2 3 cm Durchmesser schutzt die benachbarten Gewebe von Streustrahlen Bei der Rontgenbestrahlung der Augenlider wird nach Anasthesierung des Bulbus mit 1 %igem Pantocain eine in Kunststoff eingebettete Bleischale an den Bulbus angelegt Bei der Bestrahlung der Gewebe des Bulbus waren die Lider mit einem Lidspanner geoffnet

Besprechung unserer Fallen

In den letzten zweieinhalb Jahren wurden in unserem Krankenhaus insgesamt 53 Patienten mit entzundlichen Augenerkrankungen einer Kontakt – bzw Plesio Strahlentherapie – unterzogen Je nach der Diagnose lässt sich das Krankengut in folgende Gruppen gliedern

1	Dakryocystitis subac	3 Fälle
2	Blepharitis chr	5
3	Keratitis superfic	
	a Keratitis herpetiformis	4 "
	b Caustio corn	3
4	Leukoma et vascularisatio corn	7
5	Status p extr cat invasio epithel in cam ant	7
6	Scleritis recid	5
7	Uveitis recid	17 "
8	Tuberculoma iridis	1 Fall
9	Myositis musc recti ext et obl sup	1 "

Personen verminderten sich die Prazipitate nach beendeter Behandlung zahlen massig und zeigten eine deutliche Pigmentierung Wahrend der Rontgen behandlung wurde auch die seit Monaten erfolglose Lokaltherapie fortgesetzt

8 Tuberculoma Iridis

Zwei Monate vor Beginn der Behandlung war bei einem unserer Patienten mit halbseitiger seit 2 Jahren haufig rezidivierender tuberkuloser Iridocyclitis in der vorderen Kammer an der Iris ein linsengrosses gelbliches Gebilde aufgetreten das den Eindruck eines Tuberkuloms erweckte Gleichzeitig stieg der intraokulare Druck Die Linse war bis zur Kapsel trub Die Dosierung gestaltete sich wie folgt zweimal wurden 2tagig 100 r und dreimal ebenfalls 2tagig 200 r insgesamt also 800 r mit einer Tube von 1 cm Durchmesser (30 kV 20 mA Al F 0 3 FHA 15 cm) gegeben und die Strahlen unmittelbar auf das Tuberkulom gerichtet Nach der Behandlung schrumpfte das Tuber kulom auf die Halfte zusammen um einen Monat spater fast ganz abzuklingen

9 Myositis musc rect. et obl sup l u

In unserem Krankengut befand sich u a ein 56jahriger Mann mit bilateraler seit Jahren andauernder oft rezidivierender Augenmuskelenzundung Dem Patienten wurde 2tagig in einer Sitzung eine Dosis von 30–40 r auf beide Augen verabreicht (10 kV 20 mA F 0 FHA 15 cm) Gesamtdosis auf ein Auge war 170 r Nach der Behandlung verringerten sich die Schmerzen und die Augenmuskelfunktion besserte sich zusehends (Untersuchung des Doppelt sehens ergab ein normales Ergebnis) Noch vor der Strahlenbehandlung war dem Kranken Prednisolon Vitamin B_1 B_{12} Nerobolil®* und Kalium chloratum verabreicht worden die aber alle erfolglos blieben

Besprechung

Seitdem Instrumente Methoden und Dosierung der Strahlentherapie zuver lassiger geworden sind hat sich auch ihr Indikationsgebiet erweitert Die Ront genstrahlen treten in Wechselwirkung zum Organismus und fuhren zu radio chemischen und biologischen Veranderungen Die praktische Erfahrung zeigt dass die therapeutische Wirkung der Rontgenstrahlen der Erhohung der Strah lendosis nicht proportional ist

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* (Anabol Steroid)

larisation aufzuhalten (Auch bei dem am langsten beobachteten Patienten zeigte sich seit 2 Jahren keine Progression) Bei sämtlichen Patienten trat am 3 bzw 4 Tag der Behandlung an der Konjunktiva vorübergehend eine massive Hyperämie auf

5 Epitheleinwanderung in die vordere Kammer nach Starextraktion

Zur Bekämpfung der Epithelproliferation, die bei allen sieben Patienten als postoperative Komplikation in der vorderen Kammer aufgetreten war wurde Röntgentherapie eingesetzt (30 kV, 20 mA Al F 0 3 FHA 15 cm) wobei den Patienten 3 bis 4tägig eine Dosis von 50–80 r in einer Sitzung – also insgesamt 300–500 r verabreicht wurde Bei 4 Patienten schritt die Proliferation bei Verabfolgung einer Gesamtdosis unter 400 r weiter fort während bei 3 Patienten denen eine Gesamtdosis von uber 400 r gegeben wurde die Epithelproliferation zum Stillstand gebracht werden konnte (Die längste Kontrollzeit betrug 2 Jahre) Vielfach wird auch eine Gesamtdosis von 2000 r empfohlen

6 Scleritis recidivans

Bei Fallen mit verschiedener *Atiologie* die jahrelang rezidivierten und sich den usuellen Lokal und Allgemeinbehandlungen gegenüber als resistent erwiesen wurde 4tagig eine Strahlendosis von 30–50 r insgesamt 150–320 r (30 kV 20 mA Al F 0 3 FHA 15 cm) verabreicht Die zur Behandlung notwendige Fixierung des Auges geschah durch Blicklenkung und zwar so dass der *skleritische Herd in den Strahlenkegel zu liegen kam Zwei der 5* Falle zeigten keine Besserung während sich bei 3 Patienten Lokalsymptome und Schmerzen bedeutend verringerten Für die Dauer der Röntgentherapie unterblieb jede Lokalbehandlung

7 Uveitis recidivans

a Uveitis acuta 4 Falle
b Uveitis chronica 13 Falle

Unsere Patienten mit Uveitis bekannter und unbekannter Ätiologie erhielten folgende Rontgentherapie

Bei akuter Uveitis wurden 3 bis 4tagig 20–30 r insgesamt 80–180 r (30 kV 20 mA Al F 0 3 FHA 15 cm) bei chronischer Uveitis jeden dritten Tag 30–100 r (insgesamt 150–720 r) verabfolgt Nur bei Patienten bei denen die *Sehschärfe infolge eines schon bestehenden Stars* (Katarakta) schlechter war als 0 1 erhohten wir die Gesamtdosis bis uber 500 r Bei den akuten Fallen liess sich keine Besserung beobachten Was die 13 Patienten mit chronischer Uveitis betrifft war bei vieren keine sichtbare Regression festzustellen Bei 9

Personen verminderten sich die Präzipitate nach beendeter Behandlung zahlenmässig und zeigten eine deutliche Pigmentierung Während der Röntgenbehandlung wurde auch die seit Monaten erfolglose Lokaltherapie fortgesetzt.

8 Tuberculoma iridis

Zwei Monate vor Beginn der Behandlung war bei einem unserer Patienten mit halbseitiger seit 2 Jahren häufig rezidivierender tuberkuloser Iridocyclitis in der vorderen Kammer an der Iris ein linsengrosses gelbliches Gebilde aufgetreten das den Eindruck eines Tuberkuloms erweckte Gleichzeitig stieg der intraokulare Druck Die Linse war bis zur Kapsel trüb Die Dosierung gestaltete sich wie folgt zweimal wurden 2tägig 100 r und dreimal ebenfalls 2tägig °00 r insgesamt also 800 r mit einer Tube von 1 cm Durchmesser (30 kV °0 mA Al F 0 3 FHA 15 cm) gegeben und die Strahlen unmittelbar auf das Tuberkulom gerichtet Nach der Behandlung schrumpfte das Tuberkulom auf die Hälfte zusammen um einen Monat später fast ganz abzuklingen

9 Myositis musc rect. et obl sup l u

In unserem Krankengut befand sich u a ein 56jähriger Mann mit bilateraler seit Jahren andauernder oft rezidivierender Augenmuskelenzündung Dem Patienten wurde 2tägig in einer Sitzung eine Dosis von 30–40 r auf beide Augen verabreicht (10 kV 20 mA F 0 FHA 15 cm) Gesamtdosis auf ein Auge war 170 r Nach der Behandlung verringerten sich die Schmerzen und die Augenmuskelfunktion besserte sich zusehends (Untersuchung des Doppeltsehens ergab ein normales Ergebnis) Noch vor der Strahlenbehandlung war dem Kranken Prednisolon Vitamin B_1 B_{12} Nerobolil®* und Kalium *chloratum* verabreicht worden die aber alle *erfolglos blieben*

Besprechung

Seitdem Instrumente Methoden und Dosierung der Strahlentherapie zuverlässiger geworden sind hat sich auch ihr Indikationsgebiet erweitert Die Röntgenstrahlen treten in Wechselwirkung zum Organismus und führen zu radiochemischen und biologischen Veränderungen. Die praktische Erfahrung zeigt dass die therapeutische Wirkung der Röntgenstrahlen der Erhöhung der Strahlendosis nicht proportional ist

* (Anabol Steroid)

Im Wirkungsmechanismus der Strahlentherapie spielen teils lokale teils allgemeine Fakten eine Rolle Die eine Lokalwirkung ist eine lytische d h dass die labilen Zellen des Infiltrats die Lymphozyten und Granulozyten gelöst werden so dass bakteriotrope und proteolytische Fermente frei werden. Eine andere Lokalwirkung fuhrt zu aktiver Hyperämie die phagozytierende Fähigkeit der Histiozytenelemente steigert sich wodurch es zur Absorption der Infiltrate und Hamorrhagien und zur Reparation der einzelnen Lasionen kommt

Die Allgemeinwirkungen der Rontgenstrahlen bestehen darin dass die Wasserstoffionenkonzentration des Blutes und der Gewebeflussigkeiten sich in alkalische Richtung verschiebt die Elemente des Reticulozytensystems mobilisiert werden die Antikorperproduktion steigt und die Rontgenstrahlen infolge ihrer proteolytischen Wirkung auch eine indirekte aspezifische Proteintherapie *(Wint Reding)* betrachtet werden können Ein grosser Teil der Autoren behauptet daher dass die antiphlogistische Rontgenbestrahlung eine Form der aspezifischen Therapie darstellt Das wird auch dadurch bestatigt dass man nach Rontgenbestrahlungen nicht nur lokal sondern auch humoral und neural eine Veränderung im Organismus wahrnehmen kann (Der Serumalbumingehalt sinkt die Kolloidstabilitat wird gestort die Wasserstoffionenkonzentration erfahrt eine Anderung usw)

Als allgemeine Funktion der Strahlentherapie kann u a auch die schmerzstillende Wirkung angesehen werden die sich einerseits damit erklaren lasst dass die Wasserstoffionenkonzentration basisch verschoben wird anderseits damit dass die Nervenendigungen infolge der Verringerung des Gewebedruckes von der Kompression befreit werden Dazu kommt noch die Strahlenwirkung auf die neurovegetativen (besonders die sympathischen) Nervenendigungen die eine Besserung des lokalen Kreislaufs zur Folge hat (Aus diesem Grund bestrahlt *Vallebona* bei Glaukom die zervikalen Ganglia)

Leider mussen wir von einem Vergleich mit den Ergebnissen von *Boles Carenini* und Mitarbeiter absehen da die Autoren nur wenig uber ihre therapeutischen Resultate berichten und eher eine genaue Besprechung rontgentechnischer Verfahren geben und wir auch in solchen Fallen oberflachliche Strahlentherapie anwandten wo jene eine tiefe bzw halbtiefe therapeutische Technik bevorzugten Wir arbeiteten stets mit niedrigen Spannungen und mit niedrigenen Einzel bzw Gesamtdosen als die erwähnten Autoren In Ungarn wurde von *Geher* eine Mikrodosis Therapie die Methode nach *K Pape* (80 kV 6 mA Al F 3 0 FHA 40 cm 6 Sitzungen in denen je 10 r verabreicht wurden) und von *Orosz* der van der Plaatsche Apparat angewendet

Wir bevorzugten niedrige Dosen da unseres Erachtens bessere Wirkungen nicht durch eine Erhohung der Dosis erzielt werden konnen und trachteten jene minimale Dosis zu finden mit der sich schon therepeutische Resultate erreichen lassen bzw die optimale Dosis festzustellen Dabei soll bemerkt werden dass in unserer Abteilung die Rontgentherapie als eine Form der aspezifischen Reiztherapie in den meisten Fallen als Ergänzung nicht aber als

ausschliessliche Behandlung angewendet wird – Vielleicht ist es dieser Methode zu verdanken dass in den letzten zweieinhalb Jahren nur bei 2 von 53 Patienten als Nebenerscheinung eine fluchtige Dermatitis der Augenlider auftrat Als schadliche Nebenwirkung der Rontgenstrahlen sei noch die massige reaktive konjunktivale Hyperamie erwahnt die am 2 bis 3 Tag (vom Beginn der Behandlung an) aufzutreten und nie langer als 1 Woche anzudauern pflegt

Zusammenfassung

Autoren unterzogen in den letzten zweieinhalb Jahren 53 Patienten mit entzundlichen Augenerkrankungen der Plesio Therapie In samtlichen Fallen hatten sich die usuellen Arzneimittel als erfolglos erwiesen. Nach der Strahlentherapie stellte sich in 33 Fallen eine signifikante Besserung ein Ernste Nebenwirkungen liessen sich nicht feststellen Die Nahbestrahlung ersetzt die β Behandlung

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From the Department of Ophthalmology Kommunehospitalet Copenhagen Denmark
(Heads P Brændstrup and M Norn)

ENDOGENOUS UVEITIS

I Clinical Aspects

BY

M S NORN

Much work has been done to classify the aetiology of endogenous uveitis

Tuberculosis and syphilis were formerly considered to be important causes The theory of their aetiological significance has lost ground however parallel with the decreasing incidence of these diseases in the population

Bacteria are rarely detected direct in the eye *Verrey* claimed to have found staphylococci pneumococci and corynebacterial species in aqueous humour obtained by chamber puncture but no similar observations have been made by others (*Sallmann*)

The favourable effect of steroid treatment militates definitely against the view of bacteria as responsible for uveitis

Toxoplasma gondii a protozoan parasite can provoke uveitis A positive seroreaction is often seen However this reaction being also often positive in the normal population it is difficult to assess how often toxoplasma is the cause of uveitis

Toxocara a nematode worm can likewise provoke uveitis (*Ashton*)

Histoplasma is a fungus frequently occurring in certain valleys in the U S A It sometimes provokes pulmonary symptoms Some investigators take it to be a frequent cause of uveitis while others do not mainly because they have seen no instances of uveitis in fairly large series of patients with pulmonary histoplasmosis

Histoplasmosis has not been met with in Denmark but other fungal diseases

Received September 30th 1968

occur whose role as the cause of uveitis has not yet been clarified (*Aspergillus Candida albicans*)

Intestinal bacteria may perhaps play a part. *Dyster As* showed that endo toxins from certain Gram negative rods may provoke aqueous flare in rabbits

Uveitis is often associated with general diseases e g joint diseases (*Perkins*)

We do not yet know exactly how much importance may be attached to the focal theory A focus elsewhere in the organism (teeth paranasal sinuses intestine urogenital organs) may be conceived to reactivate an uveal process on an allergic immunological basis

Attention has lately been turned to the auto immune diseases (*Burns*) Hashimoto s thyroiditis is a typical representative of such diseases (antibody against the patient s own thyroid tissue) Sjogren s syndrome is supposed to be due to auto antibody against the patient s own lacrimal and salivary glands

A disease cannot however be classified as auto immune merely on the basis of observation of antibodies against the patient s own tissue (*Dieckhues*) be cause such antibodies may be conceived to develop secondarily in consequence of tissue destruction the aetiology of which is different

The aetiology can be established in only very few of the uveitis cases encountered In few instances one may have a well founded suspicion, but most often the aetiology is definitely obscure

Duke Elder concludes his exhaustive historical and topical review of the subject by maintaining that in future we shall possibly smile at our present deficient knowledge and our conjectures

The therapy of uveitis is inadequate owing to our ignorance with regard to the aetiology A specific therapy (daraprim (pyrimethamine) against toxo plasmosis elimination of foci antibiotic treatment) is rarely instituted Most often we must confine ourselves to an unspecific treatment (steroids to abate the inflammatory process mydriatics to prevent synechiae in cases of iritis) Our treatment hardly prevents recurrence

It is therefore necessary that we continue our endeavours to solve the aetiological problems We must aim at refining the serological test methods subject the aqueous humour to serological examination and compare the results of this with the serology of the blood etc (*Paul et al*)

The problem must also be attacked from other aspects (*Aronson*)

Experimental investigations have shown that three different mechanisms may be responsible for recurrence of uveitis first reactivation of a noxa present in the uvea (e g encapsulated toxoplasma) secondly occurrence of immuno competent cells in the uvea and thirdly unspecific alteration of the vascular permeability at the site of a previous focus in the uvea which may tend to cause renewed recurrence (*Aronson*)

Woods attempted to divide the cases of uveitis into two groups *viz* granul omatous and non granulomatous uveitis

From the Department of Ophthalmology Kommunehospitalet Copenhagen Denmark (Heads P Brændstrup and M Norn)

ENDOGENOUS UVEITIS

I Clinical Aspects

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Patients presenting sequelae of uveitis but no signs of active inflammation within the period concerned were not included either

The series investigated comprised 449 patients

Incidence

Of the 449 patients with uveitis 316 had their first attack within the period of 1958–1968 while 133 had had attacks before 1958 In other words we saw 316 fresh cases of the disease within a 10 year period

On an average 32 new patients with uveitis are referred annually to an ophthalmological unit serving a population of about 700 000 i e 0 05 per mille

Leira found an incidence of 0 6 per mille annually of endogenous non purulent inflammation including scleritis episcleritis and phlyctaenae The incidence of endogenous uveitis calculated on the basis of *Leira*s series is 0 4 per mille The high incidence is due in part to inclusion of all cases and not solely the fresh ones

The incidence of uveitis calculated in our Department (1 20 000) does not represent the proper incidence in the population because the uveitis patients referred to an ophthalmological unit constitutes only a certain proportion of the total number and even mainly the relatively severely affected proportion while milder cases generally are treated by ophthalmic medical practitioners

Types of Uveitis

The clinical classification of uveitis cases differs in different reports No satisfactory classification can be carried through as long as this cannot be done on an aetiological basis

Perkins performed a simple division into anterior posterior and generalized uveitis and a subdivision of these groups into acute and chronic forms i e a total of six groups The individual cases may however be difficult to classify Especially it may be difficult to differentiate between subacute and subchronic cases

I have in this paper used another less simple classification corresponding to that most frequently employed in this country and followed fairly closely in the previously published Danish report (*Vesterdal*)

The series was divided into two groups one with anterior uveitis (iritis)

In the former group the noxa is found in the uvea and in the latter elsewhere in the *organism*

Granulomatous uveitis is characterized by presence of clinically fat precipitates nodosity of the iris or elsewhere in the uvea Patho anatomically granuloma formation is noticed with epitheloid cell nests surrounded by lymphocytes

According to *Wood*, steroid treatment may be indicated for non granulomatous uveitis whereas it is supposed to be contra indicated for the granulomatous form because steroids may *aggravate the process in the eye*

Wood s classification proved not to be tenable in practice, because the clinical criteria by no means always accord with the patho anatomical Further, the indication for steroid treatment does not depend on the clinical concept of granulomatous uveitis though a granulomatous character always calls upon the therapist to consider the matter carefully before he institutes steroid treatment

The present study based on a Danish series of cases aimed specially at deciding whether the serological routine tests performed are of any value or unnecessary

The prognosis including frequency of recurrence chronicity and binocularity *is of practical importance Parameters of a possible prognostic* value have therefore been searched for

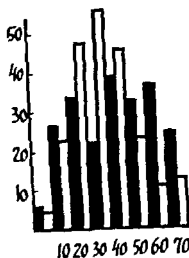
The series under review has been compared with an earlier Danish series (published by *Vesterdal* 1942–1951) and with foreign series (Northern Norwegian *Leira* British *Perkins* American *Kimura*) because the aetiology of uveitis may differ dependent on differences in time and topography

Present Material

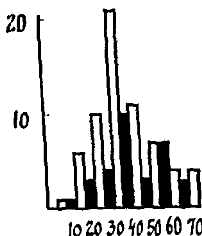
The present investigation comprised all the patients with endogenous uveitis who contacted the Department of Ophthalmology within a 10 year period (1958–1968)

The concept of endogenous uveitis may be difficult to delimit We naturally excluded traumatic uveitis *Spätinfektion* kerato uveitis and herpetic uveitis *as these may all be regarded as exogenous forms*

Phacho anaphylactic uveitis sympathetic uveitis Possner Schlossmann s syndrome serous retinopathy and Fuchs heterochromia have likewise been left out of account these diseases being of a special kind the two latter even hardly forms of uveitis



Graph I
Age at onset of uveitis all uveitis type 273 women (black columns) and 226 men (white columns)



Graph II
Acute fibrinous iritis Age at onset of uveitis 31 women (black columns) and 64 men (white columns)

Vesterdal arrived at a similar age and sex incidence though with a male maximum as early as at 25–30 years of age

Regarding subacute non granulomatous iritis males and females were equally

and the other with posterior uveitis (choroiditis) General uveitis was classified by the most severely affected section

The cases of iritis were grouped in fibrinous nodose subacute non granulomatous and chronic iritis and a small group comprising hypopyon uveitis and panuveitis

Fribrinous iritis is a condition in which fibrin is found in the chamber in forms ranging from barely visible fibrinous tracts to a massive possibly lenticular fibrinous exudate

By *nodose iritis* we understand cases of a granulomatous character, i e with presence of nodes on the iris or the pupillary border or large fatty massive precipitates

The group of *subacute iritis* comprises all non granulomatous forms of iritis with distinct light path but no fibrin

The cases of iritis running a chronic course were collected in a special group

Finally the patients with hypopyon endophthalmitis and panophthalmitis constituted a special group

The *choroiditis* cases were divided according to site into central juxtapapillary and peripheral

Like other clinical classifications the present is imperfect Many intermediate forms exist which are difficult to squeeze into this system

Age and sex incidence

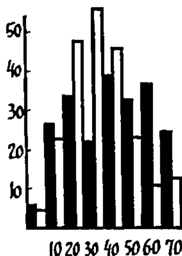
The age and sex incidence of the total series at the first attack of uveitis is shown in graph I

The number of patients with uveitis rises with increasing age to a maximum in the age group of 30–50 then to fall steadily again

The two sexes were fairly equally represented in the total series (223 females and 226 males) but there was a *preponderance of males in the age classes under 50* and a corresponding preponderance of females in the older age classes

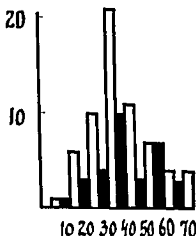
By breaking up the male and female series respectively in the different uveitis types the male preponderance in the young age groups was seen to be particularly pronounced in the group of fibrinous iritis whereas less so in that of subacute non granulomatous iritis The female perponderance manifested itself in the other types of iritis (chronic nodose) and in choroiditis

The age and sex distribution of fibrinous iritis is particularly characteristic (graph II) There were twice as many males as females Males seemed to predominate in all age groups with maximum in the age class of 30–40 years



Graph I

Age at onset of uveitis all uveitis type °23 women (black columns) and 2?6 men (white columns)



Graph II

Acute fibrinous iritis Age at onset of uveitis 31 women (black columns) and 64 men (white columns)

Vesterdal arrived at a similar age and sex incidence though with a male maximum as early as at 25–30 years of age

Regarding subacute non granulomatous iritis males and females were equally

represented but males predominated in the age classes under 50 and females in older age classes Maximum occurred in the age class of 40–50 i e later than in the case of fibrinous iritis (graph III)

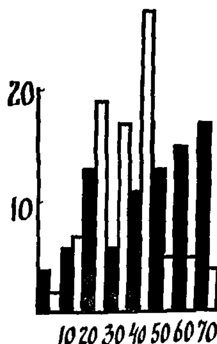
In *Vesterdal* s series there were found equally many males and females here too with feminine preponderance in the fairly old age classes, and male between the ages of 25 and 50 Maximum was noticed as early as 31–35 years of age

The two series are, thus, in fair agreement with regard to age and sex incidence, though, perhaps with maximum at a somewhat higher age in the present series than in that of *Vesterdal*

The difference observed between fibrinous and non fibrinous iritis suggests that we may be justified in sorting out the fibrinous form as a special group characterized by preponderance of males in all age classes and by maximum at a fairly young age

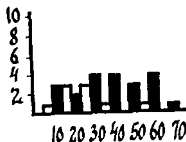
In *Haarr* s series age maximum for the total acute iritis group occurred at 40–49 In *Leira* s series at 25–45 and in Perkins series at 21–50 There was also found male preponderance in these series

Nodose iritis showed feminine preponderance in the present series The disease was equally distributed over all age classes (graph IV)



Graph III

Subacute non granulomatous iritis Age at onset of iritis 85 women (black columns) and 86 men (white columns)



Graph IV

Nodose iritis Age at onset of iritis 21 women (black columns) and 9 men (white columns)

Chronic iritis likewise presented a minor feminine preponderance The cases seemed to be equally distributed over all age classes (graph V)

The series is too small to disclose possible age maxima *Vesterdal* found maximum after the menopause whereas the other maximum about the age of 20 mentioned in the literature was not demonstrable *Perkins* noticed maximum between the ages of 31 and 50

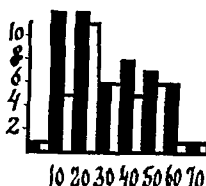
Female preponderance was likewise found by *Vesterdal Perkins* and *Leira*

Women also seemed to predominate among the choroiditis patients (53 women against 36 men (graph VI)) *Perkins* in a larger series found a more equal sex distribution (162 women and 165 men) as did also *Vesterdal* and *Leira* The cases were fairly equally distributed through with a tendency to



Graph V

Chronic irit s. Age at onset of irit s ?? women (black columns) and I men (white columns)



Graph VI
Choroiditis (all types) Age at onset of choroiditis 53 women (black columns) and 36 men (white columns)

maximum in the age class of 20–30 years This is in agreement with *Perkins* observation

The possible female preponderance in the present series was particularly pronounced within the groups of central and peripheral choroiditis (central 32 women and 25 men peripheral 12 women and 5 men)

Juxtapapillary choroiditis (Edmund Jensen) was most frequent among fairly young patients (11 patients under 30 4 over 30 and none over 60)

General Diseases

These included articular pulmonary venereal focal and other – more rarely occurring – diseases The series comprised 428 patients 21 having been excluded owing to failing information

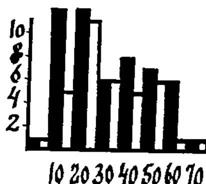
Articular Diseases

Spondylarthritis anchylopoietica (Bechterew) was demonstrated in 3 per cent of the whole series (table I) relatively most frequently in association with fibrinous iritis (9 per cent) whereas never with choroiditis Males predominated (11 men against 3 women)

Table I

General disease of 478 uveitis patients (other than venereal diseases) The figures indicate the number of patients and the bracketed figures the percentage frequency of the general disease concerned within the uveitis type in question

	fibrinous iritis	sub ac nongran iritis	nodose iritis	hypopyon panophtal	chron iritis	central chorid	juxtapap choroid	peripheral choroid	Total
ankyl poietic spondylartrit	8 (9°)	4 (3°)	0	2 (8°/)	0	0	0	0	14 (3°/)
Reiter s disease	5 (5°)	6 (4°/)	0	0	1 (3°/)	2 (4°)	0	1 (6°/o)	15 (4°/o)
Boeck s sarcoid	0	3 (? °o)	3 (9°/o)	0	2 (5°/o)	2 (4°o)	0	1 (6°/o)	11 (3°/o)
chronic polyarthrit	8 (9 o)	6 (4 /o)	0	1 (4°/)	3 (7°/o)	2 (4 o)	0	2 (1 °o)	2 (5°/)
sequelae of rheum fever	7 (7 o)	2 (1°o)	0	1 (4°)	2 (5°/o)	1 (? °/o)	0	0	13 (3°/o)
tuberculosis (sequ)	4 (4)	1 (1°/o)	2 (7°/o)	2 (8°/o)	3 (7°/o)	2 (4°/o)	0	1 (6°o)	1? (4°/o)
focal disease	8 (9°)	1 (8°o)	4 (13°/o)	3 (1?°/)	2 (5°)	8 (14 /o)	0	1 (?°o)	38 (9 o)
other general diseases	5 (5°/o)	9 (6 o)	4 (13°o)	3 (12 o)	3 (7°/o)	1 (2°/o)	2 (13°/o)	2 (12°/o)	9 (7°/o)
number of pts	91	151	30	25	39	57	15	17	478



Graph VI

Choroiditis (all types) Age at onset of choroiditis 53 women (black columns) and 35 men (white columns)

maximum in the age class of 20–30 years This is in agreement with *Perkins* observation

The possible female preponderance in the present series was particularly pronounced within the groups of central and peripheral choroiditis (central 32 women and 25 men peripheral 12 women and 5 men)

Juxtapapillary choroiditis (Edmund Jensen) was most frequent among fairly young patients (11 patients under 30 4 over 30 and none over 60)

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These included articular pulmonary venereal focal and other – more rarely occurring – diseases The series comprised 428 patients 21 having been excluded owing to failing information

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	fibrinous iritis	subac non gran iritis	nodose iritis	hypopyon panophtal	chron iritis	central choroid	juxtapap choroid	peripheral choroid	Total
ankylopoietic spondylartrit	8 (9)	4 (3 %)	0	2 (8 %)	0	0	0	0	14 (3 %)
Reiters lisease	5 (5)	6 (4 %)	0	0	1 (3 %)	2 (4 %)	0	1 (C %)	15 (4 %)
Beck s sarcoi l	0	3 (2)	3 (9 %)	0	2 (5 %)	2 (4 %)	0	1 (6 %)	11 (3 %)
chronic polyarthrit	8 (9 %)	C (4 %)	0	1 (4 %)	3 (7 %)	2 (4 %)	0	2 (12 %)	22 (5 %)
sequelae of rheum fever	7 (7 %)	2 (1 %)	0	1 (4 %)	2 (5 %)	1 (2 %)	0	0	13 (3 %)
tubercul sis (sequ)	4 (4 %)	1 (1 %)	2 (7 %)	2 (8 %)	3 (7 %)	2 (4 %)	0	1 (6 %)	15 (4 %)
focal disease	8 (9 %)	12 (8 %)	4 (13 %)	3 (12 %)	2 (5 %)	8 (14 %)	0	1 (C %)	38 (9 %)
other general liseases	5 (5 %)	9 (6 %)	4 (13 %)	3 (12 %)	3 (7 %)	1 (2 %)	2 (13 %)	2 (12 %)	2J (7 %)
number of pts	91	151	30	5	39	57	15	17	428

Vesterdal only found spondylarthritis anchylopoietica combined with fibrinous arthritis (12 per cent), but not in association with any other form of uveitis

In total uveitis series spondylarthritis anchylopoietica is reported to have occurred in 6 6 per cent (*Perl ins* 1718 patients) and 4 per cent (*Kimura* 191/ patients) The frequency is higher among patients with acute iritis 1⁹ 5 per cent (*Perkins*) 27 per cent (*Leira*) and 41 per cent of male patients (*Haarr*)

Reiter s disease (polyarthritis with associated abacterial urethritis and possibly conjunctivitis) was diagnosed in 4 per cent of the total series (13 men and 2 women) most frequently in association with fibrinous iritis (5 per cent) and non-granulomatous subacute iritis

Perl ins in a small series examined specially for this disease found it in 28 per cent of men with acute iritis *Haarr* found 2 per cent *Kimura* 0 3 per cent doubtful cases in a total uveitis series and *Vesterdal* none

A history of *rheumatic fever* was given by 3 per cent of all the patients most frequently by patients with fibrinous iritis (7 per cent) This incidence does not perhaps exceed that to be expected in the normal population (cf *Leira*) However *Perl ins* likewise found predominance of rheumatic fever among patients with iritis

Chronic rheumatoid arthritis was demonstrated in 5 per cent of the total series It was most frequent in association with fibrinous iritis (9 per cent) and peripheral choroiditis (12 per cent) but it also occurred in the other groups

Only four patients (1 per cent) were under 17 These may therefore be supposed to have suffered from juvenile polyarthritis (Still s syndrome) Two of these developed band shaped corneal degenerations

Kimura likewise found 1 per cent with juvenile rheumatoid arthritis among 1927 uveitis patients Band keratitis was present in 12 out of 13 patients

A diagnosis of adult rheumatoid arthritis was established in no more than 1 per cent of *Kimura s* cases

Vesterdal found chronic rheumatoid arthritis in 12 per cent of 350 uveitis patients fairly equally distributed over the different uveitis types

Haarr noticed chronic rheumatoid polyarthritis in few per cent only (1 6–3 / per cent)

Most investigators nowadays consider spondylarthritis anchylopoietica and Reiter s disease to be independent diseases distinct from chronic rheumatoid arthritis though the aetiology continues to be under discussion (*Kimura et al*)

In the present series spondylarthritis anchylopoietica was most often found in association with fibrinous iritis while Reiter s disease may be associated with both fibrinous iritis and subacute iritis without fibrin and chronic rheumatoid arthritis with uveitis of both the anterior and posterior sections

Uveitis thus seems to have different properties in relation to different articular diseases

Pulmonary Diseases

Boeck's disease (sarcoidosis) was diagnosed or highly suspected in 11 cases (3 per cent) The series was too small to demonstrate preference of any special uveitis type (table I)

The diagnosis was in most cases established radiographically (lungs minor long bones of hands and feet) In no more than four cases was it established histologically (two Daniell's gland biopsies one gland biopsy in relation to mediastinoscopy and one showing Boeck like changes in the ciliary body of an enucleated eye)

Vesterdal found Boeck's sarcoid *in 6 6 per cent of the cases all with uveitis* of a chronic character

Perkins noticed the disease in 3 per cent of his series Half of these cases *were acute or subacute* Only 22 *per cent presented chronic granulomatous iritis* the type stated in the literature to be characteristic of Boeck's sarcoid

Tuberculosis Signs of tuberculosis were found in 4 per cent of the series Two patients had active tuberculosis One of these suffered from granulomatous iritis and the other from uveitis with associated periphlebitis and central retinal oedema

In another 13 cases previous tuberculosis was disclosed radiographically (calcified primary complex sequela of pleuritis) These cases were distributed *over all iritis types*

Vesterdal found tuberculosis *in 4 8 per cent of her series*

It is extremely difficult to classify an uveitis clinically as tuberculosis This *can only be done in cases of acute miliary uveitis or granulomatous iritis* provided other causes are not demonstrable (*Duke Elder*)

Venereal Diseases

Venereal diseases will be mentioned in connection with a report on the serological results

Focal Diseases

Signs of focal diseases were seen in 38 patients (9 per cent) in the forms of sinusitis (1) tooth root abscesses (1.) tonsillitis (3) *and otitis (1)*

Vesterdal only found spondylarthritis anchylopoietica combined with fibrinous arthritis (12 per cent) but not in association with any other form of uveitis

In *total uveitis series spondylarthritis anchylopoietica is reported to have* occurred in 6 6 per cent (*Perkins* 1718 patients) and 4 per cent (*Kimura* 1911 patients) The frequency is higher among patients with acute iritis 19 5 per cent (*Perkins*), 27 per cent (*Leira*) and 41 per cent of male patients (*Haarr*)

Reiter s disease (*polyarthritis with associated abacterial urethritis and possibly conjunctivitis*) was diagnosed in 4 per cent of the total series (13 men and 2 women) most frequently in association with fibrinous iritis (5 per cent) and non granulomatous subacute iritis

Perkins in a small series examined specially for this disease found it in 28 per cent of men with acute iritis *Haarr* found 2 per cent *Kimura* 0 3 per cent doubtful cases in a total uveitis series and *Vesterdal* none

A history of *rheumatic fever* was given by 3 per cent of all the patients *most frequently by patients with fibrinous iritis (7 per cent)* This incidence does not perhaps exceed that to be expected in the normal population (cf *Leira*) However *Perkins* likewise found predominance of rheumatic fever among patients with iritis

Chronic rheumatoid arthritis was demonstrated in 5 per cent of the total series It was most frequent in association with fibrinous iritis (9 per cent) and peripheral choroiditis (12 per cent) but it also occurred in the other groups

Only four patients (1 per cent) were under 17 These may therefore be supposed to have suffered from juvenile polyarthritis (Still s syndrome) Two of these developed band shaped corneal degenerations

Kimura likewise found 1 per cent with juvenile rheumatoid arthritis among 1927 uveitis patients Band keratitis was present in 12 out of 13 patients

A diagnosis of adult rheumatoid arthritis was established in no more than 1 per cent of *Kimura s* cases

Vesterdal found chronic rheumatoid arthritis in 12 per cent of 350 uveitis patients fairly equally distributed over the different uveitis types

Haarr noticed chronic rheumatoid polyarthritis in few per cent only (1 6–3 ı per cent)

Most investigators nowadays consider spondylarthritis anchylopoietica and Reiter s disease to be independent diseases distinct from chronic rheumatoid arthritis though the aetiology continues to be under discussion (*Kimura et al*)

In the present series spondylarthritis anchylopoietica was *most often* found in association with fibrinous iritis while Reiter s disease may be associated with both fibrinous iritis and subacute iritis without fibrin and chronic rheumatoid arthritis with uveitis of both the anterior and posterior sections

Uveitis thus seems to have different properties in relation to different articular diseases

Pulmonary Diseases

Boeck's disease (sarcoidosis) was diagnosed or highly suspected in 11 cases (3 per cent) The series was too small to demonstrate preference of any special uveitis type (table I)

The diagnosis was in most cases established radiographically (lungs minor long bones of hands and feet) In no more than four cases was it established histologically (two Daniell's gland biopsies one gland biopsy in relation to mediastinoscopy and one showing Boeck like changes in the ciliary body of an enucleated eye)

Vesterdal found Boeck's sarcoid in 6 6 per cent of the cases all with uveitis of a chronic character

Perkins noticed the disease in 3 per cent of his series Half of these cases were acute or subacute Only 22 per cent presented chronic granulomatous iritis the type stated in the literature to be characteristic of Boeck's sarcoid

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Vesterdal found focal infection in 3 per cent among which only 5 cases of sinusitis

Leira observed pronounced radiographic signs of sinusitis in 6 8 per cent tooth root abscesses in 25 per cent, and tonsillitis in 3 1 per cent (the corresponding figures in his control series were 5 3 16 and 0 5 per cent)

Other General Diseases

Behcet s disease and Vogt Koyanagi Harada s disease were represented by one case each at most

Only few instances were found of the following general diseases uratic arthritis lupus erythematosus disseminatus scarlet fever myocarditis sepsis meningitis lymphosarcoma diabetes mellitus myasthenia gravis Burgers disease, disseminated sclerosis

Total Number of General Diseases

General diseases were diagnosed in 37 per cent of all the patients a total of 187 general diseases in 157 patients Some patients thus suffered from two or more

The general disease was in few cases only suspected to be the cause of the uveitis In other cases coincidence was demonstrated of a general disease (e g spondylarthritis anchylopoietica) and uveitis (most often fibrinous iritis) without the aetiology of the uveitis being determinable on this basis Finally in several cases concurrence of uveitis and general disease was a chance coincidence

Ophthalmic Complications

Secondary glaucoma and cataract were the most important ophthalmic complications In many instances associated affection of the optic nerve or retinal veins was noticed This was perhaps no proper complication but rather a manifestation of the uveal disease

Periphlebitis Dilated Veins

The veins were dilated bluish or there was found proper periphlebitis in 23 per cent of the total series

Pathological veins or periphlebitis was most frequent in association with choroiditis and with chronic and nodose iritis whereas much rarer in relation to fibrinous and subacute non nodose iritis (table II)

The venous system is thus affected not only in cases of posterior uveitis but also often in cases of anterior uveitis

Papillitis

Hyperaemic optic discs with blurred disc margins were observed in 10 per cent of the uveitis cases most often among those with chronic iritis and juxtapapillary choroiditis This was only natural where the latter disease was concerned because this process is situated close to the optic disc

Papillitis was rather frequent in relation to the other forms of choroiditis and nodose iritis and also relatively frequent in non granulomatous iritis but was never seen in association with fibrinous iritis in the present series

The distribution over the different uveitis types thus does not correspond exactly to the distribution of the pathological vein findings

Glaucoma

A rise exceeding 25 mm applanatory tension was shown in 87 (20 per cent) of the uveitis cases (table II) the majority patients with iritis whereas hardly ever in patients with choroiditis and relatively rarely in patients with fibrinous iritis

In most cases they were only transitory rises which fell again without treatment or in response to diamox (acetazolamide) After the uveitis had ceased the diamox treatment could be discontinued without the tension rising again

Ten patients presented iris bombé due to synechia between the iris and lens in consequence of anterior uveitis (four cases of fibrinous iritis four of non granulomatous two of nodose and one of chronic iritis)

There were nine cases of narrow angle glaucoma and ten of simple glaucoma diseases which probably most often were independent of the uveitis In the remaining 68 cases the uveitis must be supposed to have been responsible for the rise in pressure

Seventeen patients were subjected to antiglaucomatous operation two with

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Table II

Frequency of pathological veins papillitis and glaucoma (applanatory tension exceeding 25 mm most often transitory ocular hypertension) among 428 uveitis patients

	fibrin iritis	subac nongran iritis	nodose iritis	hypopyon panophtal	chron iritis	central choroid	juxtapap choroid	peripheral choroid	Total
periphlebit	2 (2 %)	9 (6 %)	7 (23 %)	4 (16 %)	8 (21 %)	9 (14 %)	5 (33 %)	15 (29 %)	49 (11 %)
path veins total	17 (18 %)	19 (13 %)	9 (30 %)	9 (36 %)	12 (31 %)	18 (32 %)	5 (33 %)	8 (47 %)	97 (23 %)
papillitis	0	14 (9 %)	4 (13 %)	1 (4 %)	9 (23 %)	8 (14 %)	3 (20 %)	2 (12 %)	41 (10 %)
glaucoma	16 (17 %)	42 (28 %)	9 (30 %)	6 (24 %)	13 (33 %)	1 (2 %)	0	0	87 (20 %)
number of pts	94	151	30	25	39	57	15	17	428

iris bombe to transfixing of the iris six to iridectomy nine to filtration operation (three to iridencleisis one to Elliot s trephining and five to Scheie s operation)

Cataract

A total of 28 patients (7 per cent of all the uveitis patients) had 36 cataract extractions performed

The average age at cataract operation was 54 a relatively young age compared with the usual for series of cataract patients In a control cataract series from our Department within the period ranging from 1955 to 1965 (*Norn* 1967) the average age was just over 70

In the series under review half of the patients were under 60 The age incidence is shown in table III

The early development of cataract was in relatively few cases due to glaucoma or sequelae of glaucoma operation In other cases the development of cataract must be supposed to have been accelerated by the uveitis itself

The cataract extraction was often undramatic Iris synechiae if present were as a rule easily detached with a spatula

Complications during or after cataract extraction were observed in ten out of 36 cases (haemorrhage in the vitreous in three loss of vitreous body in three shallow chamber in two hypopyon and secondary glaucoma in one case each)

This frequency of complications does not exceed that in the stated control series

It seemed however as if aqueous flare tended to persist longer and vitreous opacities to be more pronounced than usually in relation to cataract extraction

Table III

Age at cataract extraction 36 uveitis patients

ge	15–39	40–49	50–59	60–69	≥ 70
number of pts		6	5	15	5

Enucleation

Enucleation was performed in four cases in two owing to glaucoma and in two to painful eye without perception of light

Visual Acuity

The visual acuity was not in all cases followed throughout the course More particularly in many cases the visual acuity at the time of recovery from the disease was unknown

Table IV shows the poorest visual acuity observed during the course of illness

The patients with panophthalmia and hypopyon chronic iritis nodose iritis, and fibrinous iritis had the poorest vision whereas the vision was strikingly good in the cases with juxtapapillary choroiditis which is characterized by rarely threatening the centre

Within the group of central choroiditis cases were recorded with fairly good vision This must be due to inclusion of choroiditis near the centre in this group

Discussion

The present investigation was based on case reports Various figures must therefore be regarded as minimum values e g the number of cases with periphlebitis dilated veins etc

Unfortunately none of the patients were followed up We know the social prognosis of the uveitis patients in this country however *Bech* having in 1961 reviewed the material from the National Institute of the Blind and partially Sighted

Bech arrived at the result that in a population of 4 mill four cases are found annually of visual disabling owing to chronic iritis Other forms of uveitis are probably included in the group The original diagnosis may be difficult to establish at the final stage

The frequency of uveitis in the series under review originating from an ophthalmic unit was calculated at 1 20 000 annually Visual disabling occurs at a frequency of 1 1 000 000 annually This means that one out of 50 uveitis patients may roughly be calculated to become visually disabled

Table IV

Decreased vision of 478 patients during attack of uveitis. The figures indicate the numbers of patients and the bracketed figures the percentages of patients having the visual acuity concerned within the uveitis type in question

	fibrin iritis	subac nongran iritis	no lose iritis	hypopyon panophthal	chron iritis	central choroid	juxtapap choroid	peripheral choroid	Total
< 1/60	9 (30 %)	25 (17 %)	8 (7 %)	14 (56 %)	14 (36 %)	11 (19 %)	0	3 (18 %)	103 (24 %)
< 6/60	1 (13 %)	12 ([illegible])	5 (17 %)	1 (4 %)	7 (18 %)	10 (19 %)	1 (7 %)	1 (6 %)	49 (11 %)
< 6/18	31 (33 %)	30 ([illegible] %)	9 (7 %)	4 (16 %)	11 ([illegible] %)	15 (26 %)	5 (33 %)	2 (12 %)	106 (25 %)
< 6/9	13 (14 %)	28 (19 %)	5 (17 %)	3 (12 %)	2 (5 %)	12 ([illegible] %)	2 (13 %)	6 (35 %)	71 (17 %)
≥ 6/9	10 (11 %)	56 (37 %)	4 (13 %)	3 (12 %)	5 (13 %)	9 (16 %)	7 (47 %)	5 (9 %)	99 (21 %)
number of pts	94	151	30	25	39	57	15	17	478

Many comprehensive uveitis reports similar to the present are available in the literature A direct comparison is often impossible however owing to different clinical classifications of the various series

In the present report just as in that of *Vesterdal* fibrinous iritis has been separated out as a special group

This classification seems to be justified because fibrinous iritis differs in many respects from other types of uveitis

It is mainly found in fairly young men and often in patients with spondylarthritis anchylopoietica and Reiter s disease The disease is rarely complicated by papillitis and relatively rarely by glaucoma

The preponderance of males with fibrinous iritis might perhaps be due to its frequent combination with spondylarthritis anchylopoietica and Reiter s disease which both are most frequent in men Recognized cases of these two diseases can however only partially explain the unequal sex distribution of fibrinous iritis (male preponderance 8 cases of spondylarthritis 11 of Reiter s disease 33 of fibrinous iritis)

The frequencies of general diseases differ from one uveitis series to another This may be due in part to the diagnostic criteria employed Thus for instance, Reiter s disease was frequent in the present series while in others similar cases may have been classified as rheumatoid arthritis spondylarthritis anchylo poietica urethritis or prostatitis

The frequency noted will moreover depend on the interest and persistence displayed with regard to diagnosing special disease In the present series X ray and other examinations were generally only instituted in the cases where there was clinical indication for such

In future papers accounts will be given of the recurrence rate and results of serological routine tests carried out on the series under review

Summary

A review has been made of 449 cases of endogenous uveitis seen within a 10 year period The frequency of cases referred to an ophthalmic unit is 1 20 000

The age and sex incidence was characteristic where fibrinous iritis was concerned (young men) Nodose iritis chronic iritis and perhaps choroiditis on the other hand showed female preponderance

General diseases were diagnosed in 37 per cent spondylarthritis anchylo poietica 3 per cent (most frequent in association with fibrinous iritis) Reiter s disease 4 per cent seq of rheumatic fever 3 per cent rheumatoid arthritis 5

per cent Boeck's sarcoid 3 per cent seq of tuberculosis 4 per cent focal diseases 9 per cent

Periphlebitis and dilated veins were found in 23 per cent also in cases of anterior uveitis Papillitis occurred in 10 per cent most often in association with juxtapapillary choroiditis but never with fibrinous iritis

A rise of tension exceeding 25 mm was measured in 20 per cent The rise was most often transitory Iris bombé was found in 2 per cent

Cataract extraction was carried out in 7 per cent on an average 15 years earlier than in an otherwise normal series

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The series has been tabulated with indications of the intervals from the first attack to the latest attack at the time of the report

Leira concluded that recurrence is most frequent when the eye disease is associated with a chronic general disease (spondvlarthritis anchvlopoietica Boeck s sarcoid) or with a particularly pronounced structural alteration of the eye (chronic iritis)

In many uveitis cases the disease also develops in the contralateral eye either during the same attack or at a subsequent recurrence

The bilateral occurrence likewise seems to depend on the uveitis type

Vesterdal found the highest frequency of bilateral affection in chronic non nodose iritis (a scant four fifths of the cases) while this was less frequent in acute fibrinous iritis subacute iritis and nodose iritis (a scant one half) and still rarer in choroiditis The total series displayed a greater number of bilateral cases than of unilateral (189 against 161)

Leira found bilateral occurrence to be most frequent in the group comprising chronic iritis nodose iritis and choroiditis (56 per cent) and in that of acute iritis with associated spondylarthritis anchvlopoietica (51 per cent) while it was rarer in acute iritis without spondylarthritis

According to *Leira* bilateral or alternating presence is correlated with a high recurrence rate

Recurrence rate and bilateral occurrence seem to depend on the *diagnostic* classification of the uveitis types composition of the series investigated length of observation period etc

The prognosis of uveitis depends among other things on recurrence rate bilateral occurrence and chronicity

Perkins found 413 out of 1718 uveitis cases to be chronic A chronic course was most frequently seen in cases of posterior and especially *general uveitis*

Present material

The questions of recurrence rate bilateral occurrence and chronicitv were studied on the basis of a series of 428 uveitis patients from the Department of Ophthalmology *Kommunehospitalet* Copenhagen

In a previous paper (Norn) I have given details regarding composition of this series and the clinical aspects

Procedure

The data of the case records were transferred to punched cards

From the Department of Ophthalmology Kommunehospitalet
Copenhagen Denmark
(Heads P Brændstrup and M S Norn)

ENDOGENOUS UVEITIS

II Recurrence Rate

BY

M S NORN

At the onset of the first attack of uveitis it may be difficult or impossible to make a prognosis An apparently mild iritis may in the course of a few days develop into severe fibrinous iritis or it may preserve its mild form but then run a prolonged course

In other cases where perhaps a long series of examinations have been started immediately after the diagnosis has been made the mild iritis is seen to subside and the eye to have recovered before any results of the examinations have been achieved

The clinical picture of uveitis can give certain prognostic hints A nodose uveitis is taken to have a poorer prognosis than a non nodose Fibrinous iritis tends to run a shorter course

The different forms of uveitis show a tendency to recurrence The recurrence rate seems to depend on the type of uveitis

Vesterdal found fibrinous iritis to be the most frequently recurring type (in 58 per cent) while subacute iritis recurred in fewer cases (37 per cent) and choroiditis in still fewer (28 per cent) Her total series comprised 350 patients

Leira employed a different clinical classification of his series of endogenous non purulent ocular inflammation including 252 cases of proper uveitis

He noticed recurrence in no less than 82 per cent of the cases of acute iritis with associated spondylarthritis anchylopoietica (Bechterew) in 60 per cent of the group comprising chronic iritis and choroiditis and in only 48 per cent of the cases of acute iritis without spondylitis

Received September 30th 1968

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The patients were not summoned to a follow up but a questionaire was sent if the case record gave no information on recurrence rate or if apparently there had been no recurrence

In 104 cases the patient's ophthalmic medical practitioner was questioned while in 67 cases the questionaire was sent direct to the patient and in 14 such were sent to both the ophthalmologist and the patient

All the ophthalmologists promptly replied to the inquiry for which I offer them my best thanks

In 21 cases (4 per cent) the inquiry was not replied to These patients were therefore ruled out the original series having constituted 449 patients

The questionaire to the patient ran as follows

You have been treated previously at the Ophthalmic Clinic, *Kommunehospitalet* for iritis/choroiditis

Have you experienced recurrence of the disease?

How many times?

Which year(s)?

Did you consult an ophthalmologist on this account?

Observation period

The recurrence rate for the total series was 55 per cent In other words just over half of all the patients had one or more relapses

The observation periods for the total series ranged from 3 months to 24 years

As might be expected the recurrence rate rose with increasing observation time (table I)

Of the patients observed for not less than six years two thirds experienced recurrence

The total recurrence rate must be still higher as relapses may occur later than six years after the first attack

The table shows that an observation period of not less than six years is required to disclose a reasonable number of relapses This is a fact to which no importance seems to have been attached in previous statements

Interval between first and second attack

Half of the patients experienced the first relapse less than three years after the original attack of uveitis and one fifth within the first year (graph I)

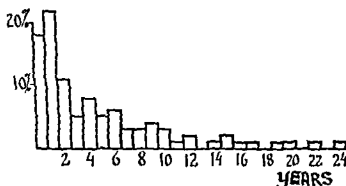
The survey comprised exclusively patients observed for at least six years and who experienced recurrence within this interval

A chance of recurrence persists for many years after the first attack The longest recurrence free interval in the present series was 24 years

Table I

The observed recurrence rate for uveitis dependence on observation period Recurrence rate in per cent The other figures of the table indicate number of patients against number of attacks chronicity freedom from recurrence and observation period

obs period	number of attacks 2	3-4	5-6	≥ 7	chronic	recurrence free	total number	recurrence rate in per cent
< 1 yr	11	0	0	0	9	28	48	23
1 2 yrs	15	10	1	0	5	31	63	41
3 5 yrs	26	12	4	2	8	39	91	48
≥ 6 yrs	44	48	27	33	34	40	276	67
Total	96	70	32	35	56	139	478	55



Graph I Recurrence rate

Time interval between first attack and first relapse in all the uveitis patients with recurrence and with an observation period of not less than 6 years (152 patients) Abscissa years Ordinate patients in per cent of total series

The risk is halved after three recurrence free years but it still exists so we cannot promise a patient permanent freedom from recurrence even after several years with no attack The risk may have been reduced to 25 per cent after six years This is however at any rate a minimum figure because the observation period often was only six years in the series under review

The patients were not summoned to a follow up but a questionaire was sent if the case record gave no information on recurrence rate or if apparently there had been no recurrence

In 104 cases the patient s ophthalmic medical practitioner was questioned, while in 67 cases the questionaire was sent direct to the patient and in 14 such were sent to both the ophthalmologist and the patient

All the ophthalmologists promptly replied to the inquiry for which I offer them my best thanks

In 21 cases (4 per cent) the inquiry was not replied to These patients were therefore ruled out, the original series having constituted 449 patients

The questionaire to the patient ran as follows

You have been treated previously at the Ophthalmic Clinic *Kommunehospitalet* for iritis/choroiditis

Have you experienced recurrence of the disease?

How many times?

Which year(s)?

Did you consult an ophthalmologist on this account?

Observation period

The recurrence rate for the total series was 55 per cent In other words just over half of all the patients had one or more relapses

The observation periods for the total series ranged from 3 months to 24 years

As might be expected the recurrence rate rose with increasing observation time (table I)

Of the patients observed for not less than six years two thirds experienced recurrence

The total recurrence rate must be still higher as relapses may occur later than six years after the first attack

The table shows that an observation period of not less than six years is required to disclose a reasonable number of relapses This is a fact to which no importance seems to have been attached in previous statements

Interval between first and second attack

Half of the patients experienced the first relapse less than three years after the original attack of uveitis and one fifth within the first year (graph I)

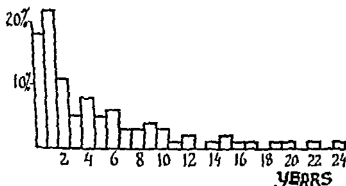
The survey comprised exclusively patients observed for at least six years and who experienced recurrence within this interval

A chance of recurrence persists for many years after the first attack The longest recurrence free interval in the present series was 24 years

Table I

The observed recurrence rate for uveitis dependence on observation period
Recurrence rate in per cent The other figures *of the table indicate number of patients* against number of attacks chronicity freedom from recurrence and observation period

obs period	number of attacks 2	3–4	5–6	≥ 7	chronic	recurrence free	total number	recurrence rate in per cent
< 1 yr	11	0	0	0	9	28	48	23
1 2 yrs	15	10	1	0	5	32	63	41
3 5 yrs	26	12	4	2	8	39	91	48
≥ 6 yrs	44	48	27	33	54	40	226	67
Total	96	70	32	35	56	139	428	55



Graph I Recurrence rate

Time interval between first attack and first relapse in all the uveitis patients with recurrence and with an observation period of not less than 6 years (157 patients) Abscissa years *Ordinate* patients in per cent of total series

The risk is halved after three recurrence free years but it still exists so we cannot promise a patient permanent freedom from *recurrence even after several* years with no attack The risk may have been reduced to 25 per cent after *six* years This is however at any rate a minimum figure because the observation period often was only six years in the series under review

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Table III

Recurrence rate number of relapses and chronicity for different uveitis types partly in the total series (428 patients recurrence rate 55 per cent) and partly among patients with observation period ≥ 6 years (226 patients recurrence rate 67 per cent) The figures indicate the number of patients except the last column which indicates the recurrence rate in per cent

	number of attacks 2	3–4	5–6	≥ 7	chronic	recurrence free	total number	recurrence rate in per cent
fibrin iritis	17	21	9	14	7	26	94	63
do obs ≥ 6 yrs	8	17	8	14	3	8	58	81
nodose iritis	2	3	6	2	7	10	30	44
do obs ≥ 6 yrs	1	1	6	2	3	5	18	55
subac iritis	46	23	11	14	0	57	151	62
do obs ≥ 6 yrs	18	13	7	12	0	12	62	81
hypopyon panoph	3	7	2	3	6	4	25	60
do obs ≥ 6 yrs	2	7	1	3	5	0	18	67
chron iritis	0	1	1	1	36	0	39	8
do obs ≥ 6 yrs	0	0	1	1	23	0	25	8
central choroiditis	15	7	4	0	0	31	57	45
do obs ≥ 6 yrs	9	5	4	0	0	12	30	60
juxtapap chor	6	3	0	0	0	6	15	60
do obs ≥ 6 yrs	2	2	0	0	0	2	6	67
periph choroid		6	0	1	0	3	17	82
do obs ≥ 6 yrs	4	3	0	1	0	1	9	89

to the other types neither from the total series nor from the smaller series observed for not less than six years

The recurrence rate seemed to be relatively low for central choroiditis and relatively high for the peripheral form

The low recurrence rate recorded for chronic iritis was due to the fact that relapses usually were referred to the chronic course

General diseases

The patients with associated joint diseases hold an exceptional position with

Age and sex

The frequency of recurrence seems to decrease with increasing age though not steadily so

The recurrence rate seems to be at a constantly high level until the age of 50 then to fall Table II illustrates the recurrence rate for all the uveitis cases with an observation period of not less than six years

The recurrence rate was perhaps a little higher for men than for women The sex difference was small however (70 per cent men and 64 per cent women)

Iritis types

Fibrinous iritis and subacute non granulomatous iritis showed a relatively high recurrence rate (table III) No definite conclusions can be drawn with regard

Table II

Recurrence rate and number of relapses among uveitis patients observed for not less than 6 years Dependence on age sex bilateral occurrence and ocular hypertension (> 25 mm) *The figures indicate number of patients Recurrence rate given in per cent*, however A total of 226 patients

patient s age	number of attacks 2	3–4	5–6	≥ 7	chronic	recurrence free	total number	recurrence rate in per cent
0–19	4	7	4	2	4	5	26	65
20–39	14	22	17	17	12	17	99	61
40–59	21	16	6	13	9	10	75	[illegible]
60–79	5	3	0	1	9	8	26	35
women	24	20	16	12	20	20	112	64
men	20	28	11	21	14	20	114	0
bilateral	14	25	20	23	26	14	122	67
unilateral	30	23	7	10	8	26	104	[illegible]
Total	44	48	27	33	34	40	226	67
ocular hypertension	9	11	5	11	11	6	53	68

Table III

Recurrence rate number of relapses and chronicity for different uveitis types partly in the total series (428 patients recurrence rate 5[illegible] per cent) and partly among patients with observation period ≥ 6 years (276 patients recurrence rate 67 per cent)

The figures indicate the number of patients except the last column which indicates the recurrence rate in per cent

	number of attacks				chronic	recurrence free	total number	recurrence rate in per cent
	2	3–4	5–6	≥ 7				
fibrin iritis	17	21	9	14	7	26	94	6[illegible]
do obs ≥ 6 yrs	8	17	8	14	3	8	58	81
nodose iritis	2	3	6	2	7	10	30	44
d obs ≥ 6 yrs	1	1	6	2	3	5	18	55
subac iritis	46	23	11	14	0	5[illegible]	151	67
do obs ≥ 6 yrs	18	13	7	19	0	12	6[illegible]	81
hypopyon panoph	3	7	2	3	6	4	25	60
do obs ≥ 6 yrs	[illegible]	7	1	3	5	0	18	72
chron iritis	0	1	1	1	36	0	39	8
do obs ≥ 6 yrs	0	0	1	1	23	0	25	5
central choroiditis	15	7	4	0	0	31	57	45
d obs ≥ 6 yrs	9	5	4	0	0	12	30	60
juxtapap chor	6	3	0	0	0	6	15	60
d obs ≥ 6 yrs	[illegible]		0	0	0	[illegible]	6	67
periph choroid	7	6	0	1	0	3	17	82
do obs ≥ 6 yrs	4	3	0	1	0	1	9	89

to the other types neither from the total series nor from the smaller series observed for not less than six years

The recurrence rate seemed to be relatively low for central choroiditis and relatively high for the peripheral form

The low recurrence rate recorded for chronic iritis was due to the fact that relapses usually were referred to the chronic course

General diseases

The patients with associated joint diseases hold an exceptional position with

Age and sex

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The recurrence rate seems to be at a constantly high level until the age of 50, then to fall. Table II illustrates the recurrence rate for all the uveitis cases with an observation period of not less than six years.

The recurrence rate was perhaps a little higher for men than for women. The sex difference was small however (70 per cent men and 64 per cent women).

Iritis types

Fibrinous iritis and subacute non granulomatous iritis showed a relatively high recurrence rate (table III). No definite conclusions can be drawn with regard

Table II

Recurrence rate and number of relapses among uveitis patients observed for not less than 6 years. Dependence on age, sex, bilateral occurrence and ocular hypertension (> 25 mm). The figures indicate number of patients. Recurrence rate given in per cent, however. A total of 226 patients

patient's age	number of attacks 2	3–4	5–6	≥ 7	chronic	recurrence free	total number	recurrence rate in per cent
0–19	4	7	4	2	4	5	26	65
20–39	14	22	17	17	12	17	99	61
40–56	21	16	6	13	9	10	75	[illegible]
60–79	5	3	0	1	9	8	26	35
women	24	20	16	12	20	20	112	64
men	20	28	11	21	14	20	114	0
bilateral	14	25	20	23	26	14	122	67
unilateral	30	23	[illegible]	10	8	26	104	6
Total	44	48	27	33	34	40	226	6
ocular hypertension	9	11	5	11	11	6	38	68

Universal antibiotic treatment was employed in 36 cases in which there was reason to suppose that a demonstrated focus might be responsible for the disease or in which the E S R was very high possibly owing to a bacterial disease

Penicillin was most frequently used Antituberculosis treatment was given in six cases

The recurrence rate was as in the total series (table V) The antibiotic therapy could accordingly not be demonstrated to have any unquestionable effect

Elimination of a possibly existing bacterial focus was attempted in 39 cases dental focus in 18 cases sinusitis in 18 tonsillitis in two and otitis in one The recurrence rate was only doubtfully reduced

Six patients had grave sinusitis Three of these experienced recurrence despite the treatment (two with fibrinous iritis and one with central choroiditis)

Four patients were treated for toxoplasmosis In one the disease persisted for two years in spite of treatment with daraprim (pyrimethamine) The toxo plasmosis neutralisation titres fluctuated between 1 50 and 1 250 and the toxo plasmosis complement fixation titres between 1 2 and 1 4)

Universal steroid treatment was carried through in 177 cases The number of cases running a subchronic or chronic course was the same as in the non steroid treated series and the recurrence rate was even higher than in the total series

Presumably it was in particular the grave cases that had been subjected to steroid treatment a fact which may account for the higher recurrence rate Steroids can mitigate the current inflammation but not prevent relapses

Summarizing we may conclude that few patients if any have received any causal treatment capable of preventing recurrence

Table V

Therapy in relation to uveitis recurrence rate number of relapses and chronicity

	number of attacks				chronic	recurrence free	total number	recurrence rate in per cent
		3–4	5–6	≥ 7				
antibiotic therapy	5	4	6	3	7	8	36	59
steroid universal	5	37	[illegible]1	19	5	45	177	6[illegible]
elimination of focus		4	4	4	4	16	39	49

regard to recurrence rate All the patients observed for six years or more experienced recurrence unless the uveitis assumed a chronic course

The recurrence rate of uveitis in association with joint diseases was 88 per cent, the highest one recorded in the present series (11 out of 12 uveitis cases with a history of spondylarthritis anchylopoietica 9 out of 10 with Reiters disease, 13 out of 15 with rheumatoid arthritis 10 out of 12 with rheumatic fever)

On the other hand recurrence free uveitis cases running a non chronic course were found among patients with Boeck s sarcoid tuberculosis syphilis gonorrhoea focal diseases and other general diseases

The total recurrence rate for these patients with general non articular diseases was 67 per cent a figure corresponding exactly to that for the corresponding total series (Table IV, cases observed for not less than six years)

A calculation for the total series with a shorter average observation time showed the same tendency

The recurrence rate was high among patients with general joint diseases (spondylarthritis anchylopoietica 79 per cent Reiter s disease 87 per cent rheumatoid arthritis 77 per cent seq of rheumatic fever 77 per cent total of joint diseases 80 per cent – 64 patients)

The recurrence rate for the total series of 428 patients was only 55 per cent

The rate was not particularly high among the patients with other general diseases It was even strikingly low (27 per cent) among cases of Boeck s disease

Therapy

A causal therapy might be expected to prevent relapses

Table IV

Recurrence rate and number of relapses in patients with associated joint diseases and other general diseases Joint diseases comprise spondylarthritis anchylopoietica Reiter s disease chronic rheumatoid arthritis seq of rheumatic fever

Observation period ≥ 6 years

	number of attacks 2	3–4	5–6	≥ 7	chronic	recurrence free	total number	recurrence rate in per cent
joint diseases	7	15	5	16	6	0	49	88
other general diseases	13	10	11	20	15	11	80	67

Universal antibiotic treatment was employed in 36 cases in which there was reason to suppose that a demonstrated focus might be responsible for the disease or in which the E S R was very high possibly owing to a bacterial disease

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Table V

Therapy in relation to uveitis recurrence rate number of relapses and chronicity

	number of attacks				chronic	recurrence free	total number	recurrence rate in per cent
		3–4	5–6	≥ 7				
antibiotic therapy	8	4	6	3	7	8	36	59
steroid universal	[illegible]	3	21	19	[illegible]	43	177	62
elimination of focus	7	4	4	4	4	16	39	49

Bilateral occurrence

By bilateral occurrence we here understand development of uveitis simultaneously or successively in both eyes

In the total series of 428 patients bilateral uveitis was found in 44 per cent. It was most frequent among cases of nodose iritis (70 per cent) and chronic iritis (64 per cent), while relatively rare in cases of juxtapapillary choroiditis (7 per cent)

In the other groups bilateral occurrence was approximately as in the total series (fibrinous iritis 47 per cent subacute non granulomatous iritis 37 per cent the hypopyon panophthalmia group 36 per cent central choroiditis 46 per cent and peripheral choroiditis 47 per cent)

The frequency of bilateral cases was higher among the patients observed for not less than six years 67 per cent of the total series

Both *Vesterdal* and *Leira* likewise found bilateral cases to be most frequent within the group of chronic iritis whereas the frequent bilateral occurrence of nodose iritis noted in the present series was not borne out in that of *Vesterdal*

Of the cases with associated *general diseases* those with spondylarthritis anchylopoietica chronic rheumatoid arthritis rheumatic fever and Reiter's disease were most frequently bilateral

Of all the cases within these groups 68 per cent were bilateral and of those observed for six years or more 71 per cent (the corresponding figures in the total series were 44 and 67 per cent respectively)

Bilateral uveitis was also frequent in patients with Boeck's sarcoid tuberculosis and syphilis but not with other general diseases (among patients with general non articular diseases 50 per cent had bilateral uveitis – 55 per cent of those observed for six years or more)

Is the recurrence rate higher for bilateral uveitis?

Within the total series recurrence was found in 63 per cent of the bilateral cases against 48 per cent of the unilateral

An observation period of at least six years on the other hand gave a recurrence rate of 67 per cent for both bilateral and unilateral cases (table II)

This suggests that relapses occur earlier in the bilateral cases but that the unilateral also are liable to recurrence

Chronic Course

A chronic course was found in 13 per cent of the total series of 428 patients and 15 per cent of 226 patients observed for not less than six years A chronic *course seemed to be most frequent among fairly old patients* (table II)

The division into different types of uveitis depends on the duration of the disease in the groups of chronic subchronic iritis and that of subacute non granulomatous iritis In the other groups the frequency of a chronic course

varies the disease being often chronic in the hypopyon panophthalmia group and fairly often in that of nodose iritis Fibrinous iritis and choroiditis rarely run a chronic course (table III)

A chronic course was seen in the presence of certain general diseases e g Boeck s sarcoid but was rare in association with joint diseases (only 12 per cent chronic)

Discussion

The frequencies arrived at in the present study with regard to recurrence and bilateral occurrence must be accepted with some reservation because they are based on data derived from a series of case reports It may however also be difficult by questioning the patient to get correct information on the number of relapses especially so if there have been many It may also cause some difficulty to decide whether a case is chronic or manifests itself by a series of relapses with doubtful activity during recurrence free periods

The figures stated for recurrence rate are minimum figures because only just over half of the patients had an observation period of at least six *years* The observation period plays an important part with regard to the number of relapses recorded

Which are the *prognostic conclusions* to be drawn from the clinical picture of uveitis at the start of the first attack?

If *fibrin is present* in the chamber the iritis will rarely become chronic but often recur

Nodose uveitis tends to become chronic and bilateral

Hypopyon uveitis and panophthalmia have a poor prognosis

Non nodose non fibrinous iritis may either develop into a chronic often bilateral iritis or it may run the course of subacute iritis with a risk of recurrence as in the case of fibrinous iritis

Central choroiditis is perhaps less liable to recurrence than the *peripheral* form *Juxtapapillary* choroiditis is rarely bilateral

The chance of recurrence and bilateral occurrence of *uveitis* is fairly great if the patient also suffers from *arthritis* This is true not only for spondylarthritis anchylopoietica as stated by *Leira* but also for patients with a history of Reiter s disease chronic rheumatoid arthritis and *rheumatic* fever

Rheumatic fever thus seems to have the same influence *on the course* of the uveitis as other joint diseases (cf *Godtfredsen)*

Spondylarthritis anchylopoietica seems to hold no exceptional position among the joint diseases in relation to uveitis

Other general diseases do not add to the risk of recurrence Bilateral uveitis is often seen in patients with Boeck s disease and tuberculosis

Elderly people seem to have a smaller chance of recurrence but perhaps there is a greater risk that the uveitis runs a chronic course

Uveitis in association with joint disease seems to behave in a special manner presumably because the organism reacts differently from the normal organism both in joints and uvea We do not know whether this is due to streptococcus allergy auto immunity, or other mechanism

Few cases if any become recurrence free after intended *causal therapy* The numerous therapeutic efforts resulted in freedom from recurrence in a very small number of patients at most after tooth extraction sinusitis treatment or anti tubercular or other antibiotic treatment

Summary

In an uveitis material comprising 428 cases 55 per cent of the patients experienced recurrence Of the patients observed for six years or more 67 per cent experienced recurrence

In half of the cases there was recurrence within three years of the first attack The longest recurrence-free interval was 24 years

The chance of recurrence was great for fibrinous iritis and subacute non nodose iritis and even greater when the uveitis was associated with a joint disease (spondylarthritis anchylopoietica Reiter s disease chronic rheumatoid arthritis and seq of rheumatic fever)

The tendency to recurrence was found to be less after the age of 50

Causal therapy prevented recurrence in very few patients if any

Bilateral uveitis was noticed to be most frequent in cases of chronic and nodose iritis

Prognostic criteria were set up on the basis of clinical characteristics

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A S H tests on a series of uveitis cases previously examined clinically (Norn A) and prognostically with regard to recurrence rate bilateral occurrence and chronicity (Norn B)

It was desired to make out whether the uveitis material differed from a normal material examined in the same laboratory *Statens Seruminstitut* Further it was aimed at elucidating whether special uveitis types might more often present raised values than others and finally whether a positive A S T or A S H reaction may be of prognostic importance

In other words this study was concentrated on clarifying if possible whether it had any purpose to continue these tests as a routine as has been done so far in the Department of Ophthalmology or whether they may be omitted in ca es of uveitis

Present material

The original series of uveitis patients comprised the total number (449) referred to the Department of Ophthalmology (Out Patient Department) *Kommune hospitalet* between 1958 and 1968

Blood samples were as far as possible drawn as a routine usually at the first consultation

313 patients were subjected to A S T test once or more and 249 of these to A S H test The reason why the number subjected to the latter test was smaller is that it was introduced later as a routine test than the A S T

A S T

Antistreptolysin titre (Oxygen sensitive haemolysin produced by haemolytic streptococci)

Age and sex

The results of the A S T tests are shown in tables I and II

The normal values regarded as reasonable on the basis of *Kalbak s* original Danish normal series *Faber s* more recent normal series and renewed controls from *Statens Seruminstitut (Faber* personal communication) are given for the sake of comparison

Of the uveitis patients 11 per cent presented pathological A S T values The

From the Department of Ophthalmology Kommunehospitalet
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ENDOGENOUS UVEITIS

III Antistreptococcal Reactions (A S T and A S H)

BY

M S NORN

Streptococci may be a direct or indirect cause of various diseases such as scarlet fever rheumatic fever acute glomerulonephritis and a number of focal diseases

Uveitis often occurs in patients with rheumatic and focal diseases (angina otitis sinusitis dental diseases)

It is therefore only natural that many consider streptococci as an important cause of uveitis

Streptococci are not present in the uveitis affected eye but a hypersensitivity to streptococci is suspected to be responsible for the uveitis *(Woods)*

Others doubt that uveitis is ever due to streptococci

A positive antistreptococcal reaction (A S T or A S H) proves that the patient has or has had a streptococcal infection Such infections being however frequent in the population a knowledge of the frequency at which the tests have been employed in the population from which the uveitis cases come is required to be able to decide whether the uveitis may be due to streptococcal infection analogously to scarlet fever for instance

The results achieved in the various laboratories are not direct comparable because the titres will depend on the procedure and standards employed

Many investigations into the A S T values in uveitis have been reported but the conclusions differ With regard to A S H on the other hand only few studies are known The conclusions of these likewise differ

The object of the present paper was to report the results of A S T and

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A S H tests on a series of uveitis cases previously examined clinically (*Norn* A) and prognostically with regard to recurrence rate bilateral occurrence and chronicity (*Norn* B)

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Of the uveitis patients 11 *per cent* presented pathological A S T values The

Table I

A S T and A S H reactions in an uveitis series The figures indicate pathological cases in per cent within the age group concerned and grouped according to sex (A S T > 200 A S H > 8000)

age	A S T				A S H			
	number of pts	percent raised	females	males	number of pts	percent raised	females	males
0– 9	5	20	33	0	4	50	50	50
10–19	41	20	13	28	37	17	10	24
20–29	65	11	15	8	39	10	7	13
30–39	59	17	21	15	42	17	17	17
40–49	58	10	11	9	52	4	6	0
50–59	46	2	0	5	40	3	1	0
60–69	26	8	10	0	24	4	5	0
70–79	13	0	0	0	11	9	0	14
Total	313	11	11	11	249	10	8	12

Table II

Frequencies of pathologically raised A S T and A S H values in uveitis series compared with a control series from *Statens Seruminstitut* (Dr *Faber*). The figures indicate percentages of pathological cases within the age group concerned.
The *reduced series* was for A S T cleared of patients with focal diseases, chronic rheumatoid arthritis and Reiter's disease and for A S H of focal diseases and chronic *rheumatoid* arthritis

age	A S T				A S H			
	number of pts	percent raised	reduced series	normal series	number of pts	percent raised	reduced series	normal series
< 5	3	0	0	0	[illegible]	50	0	0
5-17	27	19	21	15	24	17	18	15
17-60	244	11	11	10	188	9	9	5
> 60	39	5	0	0	35	6	4	0 or few
Total	313	11	10		249	10	9	

Table I

A S T and A S H reactions in an uveitis series The figures indicate pathological cases in per cent within the age group concerned and grouped according to sex ($AST > 200$ $ASH > 3000$)

age	AST				ASH			
	number of pts	percent raised	females	males	number of pts	percent raised	females	males
0–9	5	20	33	0	4	50	50	50
10–19	41	20	13	28	37	17	10	24
20–29	65	11	15	8	39	10	7	13
30–39	59	17	21	15	42	17	17	17
40–49	58	10	11	9	52	4	6	0
50–59	46	2	0	5	40	3	4	0
60–69	26	8	10	0	24	4	5	0
70–79	13	0	0	0	11	9	0	14
Total	313	11	11	11	249	10	8	12

Table III

Antistrept coccus titres in relation to different general diseases The figures indicate the percentages of patients with pathological values within different general diseases

	A S T		A S H		A S T and A S H raised simultaneously	
	total number	percent raised	total number	percent raised	total number	percent raised
chron rheumat arthrit	15	13	12	25	12	8
spondyl anchylop etica	12	8	7	0	7	0
seq of rheum fever	9	11	5	0	5	0
Reiter s disease	11	18	8	0	8	0
focal diseases	36	17	28	4	28	4
Total	313	11	249	10	249	4

values agreed approximately with those of the normal series with a corresponding age curve *No cases before the age of 5 years* maximum number between 5 and 17, and none after the age of 60

The figures tended to be *slightly higher than those of the normal series but* the difference is not significant

Neither the present nor the normal series showed any significant sex difference

The conclusion must therefore be warranted that with regard to A S T values the uveitis material did not differ unquestionably from a normal material examined in the same laboratory by the same technique and within the same period

This conclusion is inconsistent with the results of various investigations published

Vesterdal found a raised A S T in a larger proportion of her uveitis patients (19 5 per cent) than did *Kalbak* in his corresponding normal series (6 per cent)

Schone found an average A S T titre of 119 in a Norwegian series of uveitis patients against only 74 in a control series of blood donors The difference was significant

Leopold likewise found raised values The result is given *in index of range* difference which in one figure indicates the difference between uveitis series and control series An index of 100 would be ideal the method being infallible for separating pathological cases from normal An index of 50 means that the method is of no diagnostic value

Leopold arrived at a fairly good index of range difference 60 8 at a titre value of 48

Woods felt so convinced of the *aetiological role of the streptococcus in non* granulomatous uveitis that his treatment consisted in desensitisation to *streptococci*

Paul considered streptococci to be of aetiological importance in some cases of uveitis

Bjork on the other hand found no raised A S T values in a Swedish series of uveitis cases There was no proper control series

Leira noticed no signifikant difference between his uveitis cases *and his controls* (A S T above 200 in 31 9 per cent of uveitis patients and 26 6 per cent *of controls)*

Coles noted only slight differences between 68 uveitis patients (a total of 301 A S T tests) and 96 controls especially as regards the high titres He concluded in agreement with *Hogan* that no causal relation exists between streptococci and uveitis

Hallett found the average *A S T titre to be lower if anything* among uveitis cases (24) than in a series of normal controls (31) The index of range diffe

Table II
Intist ept c ccal titres within different uveitis types

	A S T		A S H		A S T and A S H raised simultaneously	
	total number	percent raised	total number	percent raised	total number	percent raised
ac fibrinous iritis	C9	19	[illegible]	11	56	7
sul ac n n gran iritis	90	13	81	11	7?	4
n l c iritis	25	4	19	11	19	0
l]{ opyon panuveitis	0	0	14	7	14	0
chron. iritis	16	0	5	0	?3	0
central choroiditis	C4	9	47	11	41	7
juxtapap choroiditis	17	6	13	0	1?	0
periph choroiditis	14	21	14	7	12	8
Total	313	11	249	10	[illegible]49	4

rence was only 45 3, i e completely unsatisfactory

The A S T titre was often followed during the course and was found to *remain unchanged during the different stages of uveitis*

General diseases

A raised A S T may be expected in a number of general diseases associated with uveitis

As seen in table III such raised A S T values were measured in cases of focal diseases Reiter s disease and perhaps chronic rheumatoid arthritis

Spondylarthritis *anchylopoietica (Bechterew) on the other hand* gave no raised A S T values this disease being exceptional among the joint diseases Sequelae of rheumatic fever also showed normal values a fact which was due to a long time interval between the original rheumatic fever and the subsequently developing uveitis

Many investigators have excluded uveitis patients with a possible streptococcal infection from their A S T report This may in fact involve ruling out of streptococcus induced uveitis cases whose existence it has been desired to prove or disprove

On the other hand it may be difficult to compare a pure normal series with one charged with unquestionable streptococcal diseases outside the uvea

Table II gives a summary of the present series cleared of the charging diseases focal diseases Reiter s disease and chronic rheumatoid arthritis

As might be expected the A S T values of this latter series were even closer to those of the control series though still with a tendency towards preponderance of pathological values

Uveitis types

Streptococci are possibly of aetiological importance within certain clinical uveitis types As shown in table IV the A S T values are perhaps raised in cases of acute fibrinous non granulomatous iritis The numbers are too small for definite conclusions to be drawn

In the literature we find quite different – likewise often rather reserved – conclusions

Vesterdal found the greatest number of positive A S T reactions in relation to subacute iritis (28 8 per cent) and the smallest number to acute fibrinous iritis (14 1 per cent) in other words the reverse results to those of the present study

Leira noticed a raised A S T in the group comprising chronic iritis and choroiditis

Table VI

Anti-streptococcus titre and prognosis (Poorest visual acuity recorded of uveitis affected eye, recurrence rate, chronicity and bilateral occurrence)

	A S T		A S H		A S T and A S H raised simultaneously	
	total number	percent raised	total number	percent raised	total number	percent raised
Vis < 1/60	72	15	52	13	59	6
< 6/60	41	2	37	6	31	3
< 6/18	90	13	66	9	60	3
< 6/9	62	8	5	8	52	2
≥ 6/9	58	14	47	11	47	6
no recurrence	90	13	73	8	73	3
2 attacks	76	9	65	12	65	5
3–4 attacks	49	18	41	17	41	12
5–6 attacks	25	8	16	17	16	0
≥7 attacks	30	10	22	0	22	0
chronic	43	5	32	0	32	0
bilateral	130	11	117	11	117	4
Total	313	11	249	10	249	4

Table V
Antistreptococcus titre in ophthalmic complications

	A S T		A S H		A S T and A S H raised simultaneously	
	total number	percent raised	total number	percent raised	total number	percent raised
periphlebitis dilated veins	85	15	79	11	79	8
papillitis	34	15	27	7	27	7
glaucoma	52	4	38	5	38	0
Total	313	11	249	10	249	4

Table II
Antistreptococcus titre and prognosis (Poorest visual acuity recorded of uveitis affected eye, recurrence rate, chronicity and bilateral occurrence)

	A S T		A S H		A S T and A S H raised simultaneously	
	total number	percent raised	total number	percent raised	total number	percent raised
Vis < 1/60	72	15	52	13	52	6
< 6/60	41	2	37	6	31	3
< 6/18	80	13	66	9	66	3
< 6/9	62	3	52	8	59	2
≥ 6/9	58	14	47	11	47	6
no recurrence	90	13	73	8	73	3
2 attacks	76	9	65	12	65	5
3–4 attacks	49	18	41	17	41	12
5–6 attacks	25	8	16	17	16	0
≥7 attacks	30	10	27	0	22	0
chronic	43	5	32	0	32	0
bilateral	150	11	117	11	117	4
Total	313	11	249	10	249	4

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	total number	percent raised	total number	percent raised	total number	percent raised
periphlebitis dilated veins	85	15	79	11	79	8
papillitis	31	15	27	7	27	7
glaucoma	52	4	38	5	38	0
Total	313	11	219	10	249	4

It is shown in table II that the A S H values relatively often were raised among uveitis cases though with no significant difference from the normal series The age variations corresponded to those of the normal series except in the group under 5 years of age which however within the uveitis series contained no more than two cases

There was no unquestionable sex difference

As was the case for the A S T values raised A S H values were found to be more frequent among the uveitis patients than in the corresponding normal series but the difference was not significant *The series of uveitis cases did not differ significantly from the normal*

This result is in disagreement with that of *Leopold* who using the mucin clot method found a raised A S H in 29.3 per cent of the uveitis patients against only 5.5 per cent of the controls The stated index of range difference was 64 4 or better than that for the A S T test

Hallett et al noticed a just significant difference between the A S H values by the mucin clot method the index of range difference being 61 8 Using the turbidimetric method on the other hand *Hallett* observed no difference between uveitis patients and controls

Coles considered the A S H reaction to be less specific than the A S T reaction

The turbidimetric method employed in the present study which must be regarded as more exact than the mucin clot method *(Faber)* revealed no significant difference between the uveitis series and the control series though the former tended to contain a greater number of pathological cases

General diseases

Within the series under review the A S H seemed to be raised in the chronic rheumatoid arthritis group which possibly included cases of secondary polyarthritis In the cases of Reiter s diseases – where the A S T was raised – the A S H was not raised Neither was it raised in relation to spondylarthritis an hylopoietica or sequelae of rheumatic fever The numbers of cases in these groups were small however (table III)

By clearing the uveitis series of cases with such general diseases as are known by experience to give raised A S H values (focal diseases and chronic rheumatoid arthritis) values were obtained corresponding even more closely to the normal (table II)

Uveitis types

The differences in A S H values between the various uveitis types were few and not significant (table IV)

Paul and *Coles* observed a tendency towards a raised A S T in posterior uveitis

Perkins found a doubtfully raised A S T in cases of chronic anterior and chronic generalized uveitis.

Thus disagreement and confusion prevails regarding the question of a relationship of A S T to certain uveitis types

Ophthalmic complications

A raised A S T might be conceived to be a sign of ophthalmic complications.

The A S T seemed to be raised in cases with dilated bluish retinal veins or cases of periphlebitis (table V)

A positive A S T reaction was perhaps more frequent in cases with involvement of the optic nerve (papillitis) than in the other uveitis cases

A *raised intra occular pressure* (above 24 mm by *applanation tonometry*) during the uveitis or even secondary glaucoma was recorded in some cases A raised A S T was not found more frequently among the cases with this complication

The poorest visual acuity recorded for the uveitis affected eye during the course of the disease *is shown in table* VI

No correlation was detected between impaired vision and A S T value

Recurrence rate

As seen in table VI there was no correlation between the A S T value and the number of relapses of uveitis The A S T reaction was not particularly often recorded as positive in cases of chronic or bilateral uveitis

There was in other words no evidence to suggest a higher recurrence rate among the possibly streptococcus induced uveitis cases owing to activation of *a streptococcal focus or to hypersensitisation to streptococci*

A S H

Antistreptohyaluronidase titre shown by the turbidity reducing method

Age and sex

The normal values are based on *Faber s* material and subsequent control material (from *Statens Seruminstitut (Faber* personal communication))

It is shown in table II that the A S H values relatively often were raised among uveitis cases though with no significant difference from the normal series The age variations corresponded to those of the normal series except in the group under 5 years of age which however within the uveitis series contained no more than two cases

There was no unquestionable sex difference

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By clearing the uveitis series of cases with such general diseases as are known by experience to give raised A S H values (focal diseases and chronic rheumatoid arthritis) values were *obtained* corresponding even more closely to the normal (table II)

Uveitis types

The differences in A S H values between the various uveitis types were few and not significant (table IV)

Hallett likewise found no raised A S H values in relation to any definite uveitis type

Ophthalmic complications and prognosis

As was noticed for A S T raised A S H values were perhaps more frequent among patients with associated periphlebitis and dilated veins

The A S H bore no relation to papillitis or glaucoma (table V)

The A S H likewise bore no relation to poorest vision of uveitis affected eye, recurrence rate chronicity or bilateral occurrence

A S T ⊂ A S H

Concurrence of pathological A S T and A S H values in the same patient

Tables III to IV show the results for the patients who reacted positively to both tests i e had or had had a streptococcal infection causing production of antibodies against both streptolysin and streptococ hyaluronidase

Both reactions were often positive simultaneously in cases of chronic rheumatoid arthritis and perhaps also focal diseases whereas not in cases of spondyl arthritis anchylopoietica Reiter s diseases or sequelae of rheumatic fever

They were often both positive in relation to acute fibrinous iritis and likewise in relation to periphlebitis and occurrence of dilated retinal veins

The figures are too low to disclose a possible correlation to visual impairment recurrence rate or chronicity

In the above reports the limits of definitely pathologically raised A S T (above 200) and A S H (above 8000) were employed

Similar conclusions could be drawn from a corresponding report including doubtfully raised values (A S T 200 or higher A S H 4000 or higher)

Discussion

Many and fairly comprehensive investigations have been undertaken into the question of a possible streptococcal aetiology of uveitis The results differ however and the hypothesis that streptococci may be an essential cause of uveitis has not yet been proved nor disproved

The difference may be due among other things to the composition of the

individual series as well as to the serological technique and the control series employed

Sufficient attention has not been given to the fact that the series of uveitis patients and that of controls should be compared within the individual age groups because the streptococcus reactions are definitely age determined

The hope had been entertained that the A S H test might give a more exact answer than the current A S T tests

The results achieved in the present series where both A S T and A S H tests were employed were disappointing in this respect Positive reactions of a patient to both tests likewise seemed to give no more exact information

The A S T reaction was tested in *aqueous humour* in an attempt to demonstrate a possible streptococcus induced disease of the eye

The titre value may however rise in the aqueous humour owing to destruction of the blood aqueous humour barrier in uveitis

It has therefore been necessary to follow the quotient between the A S T titre in the aqueous humour and that in serum according to *Goldman Witmer*

A raised quotient suggests antibody production against streptococcal exotoxin in the uvea and a low quotient is perhaps suggestive of an increased consumption of antibody in the eye (*Remky*)

The studies made so far on the A S T in aqueous humour have given no clarification of the role of streptococci in uveitis *Laffers* estimated that 5 7 per cent of all uveitis cases are due to streptococci

Hallett never found a positive A S H reaction in the aqueous humour of uveitis patients

A possible streptococcal aetiology might be conceived to influence special uveitis types

A detailed division of the present series into clinical uveitis types seemed to show that acute fibrinous iritis often is due to streptococci This hypothesis was however contradicted by the result of the A S H test and by series in which another type of uveitis displayed the most frequent occurrence of antibody against streptococci

A more or less certain predominance of antibodies against streptococci is found in most uveitis series

Uveitis patients might produce antibodies in general because of altered reactions of the organism also to the streptococcal infection that is frequent in the population and which perhaps after all has no aetiological influence on uveitis

A streptococcal focus might be the cause of frequent relapses of uveitis and if so be accompanied by a raised streptococcus titre

However in the present series no correlation was detectable between a raised A S T or A S H and frequent relapses

The frequent occurrence of positive A S T or A S H reactions in the pre

sence of periphlebitis or dilated veins suggests that these venous disorders are found particularly in association with streptococcal infection perhaps as an indication of allergy to streptococci

The series is however, too small to allow of any conclusions

In the present uveitis series antibodies against streptococci were noticed in cases with a simultaneously recognized focal disease and in chronic rheumatoid arthritis whereas not in patients with spondylarthritis anchylopoietica or sequelae of rheumatic fever Reiter s disease gave a raised A S T but no raised A S H

The present study gave a fairly negative result The series under review possibly presented a minor preponderance of cases with seroreaction to pathogenic streptococci but the figures did not differ significantly from those of a corresponding control series

The result is indicative that streptococci played an aetiological role in only few cases if any

Routine A S T and A S H tests seem not to be indicated in practice

A positive reaction to the test has no influence on the treatment nor does it give any information of prognostic value

A positive reaction may intensify the suspicion of a streptococcal focus which should be removed or treated by antibiotics

Such treatment seems however to be of importance in few instances only (*Norn* B) and do not indicate the tests except on special suspicion

It may be desirable to make the tests on suspicion of joint diseases to contribute towards the differential diagnosis of these

In general we may conclude that A S T and A S H tests rarely are of any practical importance in relation to examination of uveitis patients and that accordingly these tests can very well be spared among the blood tests which ought to be made as a routine in such cases (cf *Hogan*)

The results of the other laboratory tests made on the present uveitis series among which streptococcus agglutination titre will be reported in a future paper The latter test was not included in the present study because the reaction was not regarded as one against streptococci but rather as an unspecific reaction recording alterations of the serum proteins

Summary

The antistreptolysin titre was tested in 313 uveitis patients and the antistreptohyaluronidase titre in 249 of these

Antibodies against streptococci were perhaps found a little more frequently in this series than in the corresponding control series but the difference was not statistically significant

Streptococci thus seem to be the cause of uveitis in few cases only if any

No prognostic conclusions can be drawn from a positive titre (chance of recurrence chronic course bilateral occurrence complications)

A positive titre was found to be more frequent in patients with associated focal diseases chronic rheumatoid arthritis and perhaps periphlebitis

In practice there is no reason for routine A S T and A S H tests in cases of uveitis

Acknowledgement

My thanks are due to Professor Viggo Faber M D., Head of the Auto-Immune Department *Statens Seruminstitut* Copenhagen, for valuable aid and guidance

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A positive reaction to the test has no influence on the treatment nor does it give any information of prognostic value

A positive reaction may intensify the suspicion of a streptococcal focus which should be removed or treated by antibiotics

Such treatment seems however to be of importance in few instances only *(Norn* B) and do not indicate the tests except on special suspicion

It may be desirable to make the tests on suspicion of joint diseases to contribute towards the differential diagnosis of these

In general we may conclude that A S T and A S H tests rarely are of any practical importance in relation to examination of uveitis patients and that accordingly these tests can very well be spared among the blood tests which *ought to be made as a routine in such cases (cf Hogan)*

The results of the other laboratory tests made on the present uveitis series among which streptococcus agglutination titre will be reported in a future paper The latter test was not included in the present study because the reaction was not regarded as one against streptococci but rather as an unspecific reaction recording alterations of the serum proteins

Summary

The antistreptolysin titre was tested in 313 uveitis patients and the antistreptohyaluronidase titre in 249 of these

Antibodies against streptococci were perhaps found a little more frequently *in this series than in the corresponding control series* but the difference was not statistically significant

Christian Medical College Hospital Vellore India

INCIDENCE OF SUBCONJUNCTIVAL CYSTICERCOSIS

D K SEN and A THOMAS

Man acquires cysticercosis by ingesting the eggs usually in food or water contaminated by the excreta of an infested person and occasionally through autoinfection by anus to mouth transmission The eggs hatch in the upper intestine and as in the pig the embryos travel by the vascular or lymphatic circulation to the tissue where they develop into larvae the *cysticercus cellulosae*

The condition has world wide distribution but it is very rare except in highly endemic areas It used to be relatively common in Central Europe (*von Graefe* 1866 *Laigner Terrasse* 1932 *Toulant* 1939 *Lech* 1949) In India cysticercosis is common in pigs but infrequent in man (*Maplestone* and *Bhaduri* 1937) This is perhaps because the population here is by and large vegetarian and the non vegetarians prefer meat other than pork on religious ground

Present Study

Out of 17 000 cases attending the eye O P D over a period of 9 years we came across only 14 cases of cysticercus cellulosae Table I gives age and sex distribution of all the cases Of these 12 were subconjunctival one intravitreal and one in the anterior chamber Table II *gives the location of the subconjunc*

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Reprint request to M A Medical College Eye Dept New Delhi (India)

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Fig 1

Body of Cysticercus Larva removed from under the conjunctiva showing characteristic tortuou Lumen × 30

Comments

Cysticercus cellulosae has been found in all parts of the eye and its adnexa The western authors have reported it to be very much less common in the sub conjunctival tissue *von Graefe* (1866) saw 90 cases of cysticercosis out of 60 000 eye cases and gave their localization as subconjunctival 5 subretinal and intravitreal 80 other situations 5 *Laigner Terrasse* (1932) reviewed 35 cases and in his series the localization was subconjunctival 7 subretinal and intravitreal 26 other situations 2 Troulant (1939) reviewed 420 cases of cysticercosis in the eye out of which only 92 were subconjunctival 296 sub retinal and intravitreal other situations 32 *Lech* (1949) found only 9 5 % of their cases to be subconjunctival *Duke Elder* (1965) also stated that ocu ar cysticercosis is much less common in the subconjunctival situation But in India this incidence is strikingly different Out of 14 cases of Ocular cysti cercosis on record in the Government Ophthalmic Hospital Madras 11 were subconjunctival Siva Reddy and Satyendran (1964) reported 10 cases of which 6 were subconjunctival *Pao et al* (1967) reported 15 cases of which 13 were subconjunctival In the present series of the 14 cases 12 were subconjunctival We do not know of any anatomic or physiologic reason to explain this regional difference in the incidence which is so striking Preponderance of the affection

Table I

Age & Sex Distribution of all the cases

Sex	0–5 Yrs	6–10 Yrs	11–15 Yrs	16 20 Yrs	21–25 Yrs	26–30 Yrs	Total
Male	1	1	2	0	1	2	7
Female	0	3	1	3	0	0	7
Total	1	4	3	3	1	2	14

Table II

Localization of Subconjunctival Cysts

Upper Quadrants	Lower Quadrants	Medial Quadrants	Lateral Quadrants	Total
1	2	7	2	12

tival cysts The medial quadrant in relation to the medial rectus muscle was the most common site The patients with subconjunctival cysts came to the hospital because the hemispherical swelling in the white of the eye looked cosmetically disfiguring There was no pain or tenderness except in two cases where the presence of the cyst excited inflammatory reaction severe enough to cause suppuration Only one eye was involved in all the cases and there was one cyst in the eye Left eye was more commonly affected than the right Of the 12 cases left eye was affected in 8

A presumptive diagnosis of cysticercus cyst was made in all the cases except in two where it presented as subconjunctival abscess All the cysts were removed surgically During operation it was found that all the cysts were in intimate relation with the superficial fibres of the recti muscles Careful dissection was therefore carried out to avoid injury to the muscle fibres On removal the mass was seen to consist of an outer fibrous capsule formed by mild inflammatory foreign body reaction in the surrounding tissue Post operative period was uneventful there was no limitation of ocular movements Diagnosis was confirmed in all the cases by histopathological examination of the cyst which showed tortuous lumen of the larval body with suckers and hooklets

Acknowledgement

Our thanks are due to the medical superintendent Christian Medical College Hospitals Vellore and Prof Roy Ebenezer for their kind permission to make use of the hospital records

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Table III

Author	Year	Total Ocular Cases	Subconj Cases (%)
Incidence in continent			
von Graefe	1866	90	5 (5.5%)
Laigner – Terrasse	1932	35	7 (20.0%)
Troulant	1939	420	92 (21.9%)
Lech	1949		(9.5%)
Incidence in India			
Govt Hospital record Madras	1924	14	11 (78.5%)
Reddy & Satyendran	1964	10	6 (60%)
Rao et al	1967	15	13 (86.6%)
Sen & Thomas (Present Series)		14	12 (85.5%)

on the left side is probably because of the fact that left common carotid artery takes off directly from arch of the aorta. The intimate relationship of the cysts with the recti muscles also indicates that the embryos travel mostly by vascular circulation.

Duke-Elder (1965) has also mentioned that these cysts are usually painful on pressure and therefore may be differentiated from hydatid cysts which excite no inflammatory reaction. Our experience however is very different. The cysts were usually painless on pressure and there were no clinical evidence of any inflammation excepting in two cases. It is also interesting to note that history of having eaten pork was available in only two cases. In none of our cases stool was found to be positive even after repeated examinations and blood count showed no eosinophilia. They are therefore unreliable guides.

Summary

Twelve cases of subconjunctival cysticercosis are presented. Its incidence has been found to be very much higher in India as compared to that in the Western countries. Left eye was found to be more commonly involved. The cysts were found to be painless in majority of the cases. It is advocated that all cysts removed from under the conjunctiva be subjected to histopathological examination to establish the correct diagnosis.

Acknowledgement

Our thanks are due to the medical superintendent, Christian Medical College Hospitals Vellore and Prof Roy Ebenezer for their kind permission to make use of the hospital records

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(Head S Ry Andersen)

THE ULTRASTRUCTURE OF THE ACINI OF THE HUMAN LACRIMAL GLAND

BY

J EGEBERG and O A JENSEN

Ligth microscopic studies reveal the lacrimal gland to be of the tubulo alveolar type its secretory portions being provided with cells resembling those of the serous salivary glands

Throughout the years the human lacrimal gland has been the object of many light microscopic studies

Ito & Shibasaki (1964) have summarized these studies at the same time undertaking a light microscopic study of the orbital portion of the gland in five individuals They concluded that morphologically acini contain two types of cell i e glandular cells with smaller secretory granules (K cells) and with larger secretory granules (G cells) Furthermore the staining properties of the granules vary and the extension of the Golgi apparatus in the two types of cell is different The G cells outnumber the K cells Myo epithelial cells are found both in the terminal portions and in the small interlobular and intra lobular excretory ducts between the glandular cells and the basement membrane

Kobayashi (1958) studied the human lacrimal gland by means of the electron microscope He found different electron density of the secretory granules in man and rabbit and a different appearance of the endoplasmic reticulum whereas the granules and the Golgi apparatus were closely related in both species

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The lacrimal glands of rat rabbit and guinea pig have been studied under the electron microscope

In rats *Scott* & *Pease* (1959) found two types of secretory granule i e mucoid granules in the acinar cells which are found near to the Golgi apparatus and zymogen granules both in the acinar cells and in the epithelium of the intercalated ducts not related to Golgi vacuoles

In the same species *Ichikawa* & *Nakajima* (1962) however found only one type of secretory granule surrounded by a thin membrane probably derived from the Golgi apparatus

In guinea pigs *Chang* (1964) found mucinous granules only which were PAS positive In addition he found a highly developed Golgi apparatus with numerous small granules The same type of granule is found in the epithelial duct cells the cytoplasm of which is more dense than that of the acinar cells

In the rabbit *Kobayashi* (1958) and *Obayashi* (1959) both found four types of cell in the acini characterized by different organelle contents and an additional fifth type of cell in the excretory ducts. *Kobayashi* (1958) suggested that the four types of cell in the acini might reflect only different functional capacities in the same type of cell

Independent of the type of object examined all the authors found myo epithelial cells between the basement membrane and the acinar cells *Obayashi* (1959) found those cells on the lateral surface of the cells and *Chang* (1964) observed myo epithelial cells in the excretory ducts Indeed the latter author found two types of myo epithelial cell with a light and a dark cytoplasm respectively

The above studies indicate that the ultrastructure of the lacrimal gland may vary from one species to another The motivation for carrying out the present study was partly the desirability of obtaining further clarification of this condition partly the few available reports on investigations concerning the ultra structure of the human lacrimal gland

Material and Methods

The materi l stu lied consisted of tissue originating from lacrimal glands removed in connex on with enucleation of the eyeball in three patients (two females ?3 and 59 years old and one male 9 years old) The h stological diagnoses in the three cases were buphthalm os malignant melanoma of the choroid and glaucoma

Immediately after removal of the gland small pieces of tissue were *fixed* in 6 5 per cent glutaraldehyde buffered to pH 7.3 with sod um cacodylate *Post fixation* was carried out in ? per cent osmium tetroxide and after dehydration in ethanol the speci mens w re embed led n Ep n 81 (*Li ft* (1961)) Ultrathin sections were cut on an LKB ult at me sta ned with alkal ne lead citrate (*Reynolds* (1963)) and examined in a Ph lips EM 100 B electron microscope

Results

Notwithstanding the fact that the glands studied originated from patients with different eye diseases and in spite of the great difference in the age of the patients no qualitative differences could be demonstrated between the acini studied in the three glands neither by light microscopy nor by electron microscopy In particular no pathological changes were found by light microscopy

There were two types of cell in the acini secretory cells and myo epithelial cells the latter being located in the basal portions of the acini (Fig 1)

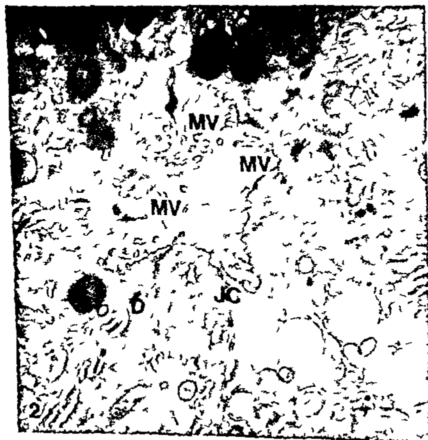


Fig 1

Survey of an acinus in a human lacrimal gland The glandular cells are triangular in outline with the bases facing the basement membrane (BM) The intercellular spaces (IC) are conspicuous and filled with a light content In the luminal parts of the cells many secretion granules (C) are seen.

MY myoepithelial cell N nucleus Red 51 per cent from 11 ,00 X

The glandular cells These were tall and cone shaped and their broad bases were separated from the connective tissue between the acini by a relatively thick (0 5 μ) homogeneous basement membrane Their apex faced the lumen of the acinus Connexions between the individual glandular cells were established by means of desmosomes along the lateral borders of the cells (Fig 2) In between the desmosomes the cells were separated by relatively broad (up to 2 μ) intercellular spaces which were crossed by a network of numerous finger shaped outgrowths (Figs 1 and 3) On tangential sections through the acini it



Fi 9

Towa ds the lumen of the acinus the plasma membranes of the acinar cells are equipped w th se ral irr gular m crovilli (MV) and the individual cells are linked together by me ns of jun t nal c mplexes (JC) and desmosomes (D) At the same time this arran gem nt w ll clos the ntercellular spaces In the lumen circular membranes are seen re embl ng the membranes surrounding the secretion granules

Red 51 per cent from 13,500 ×

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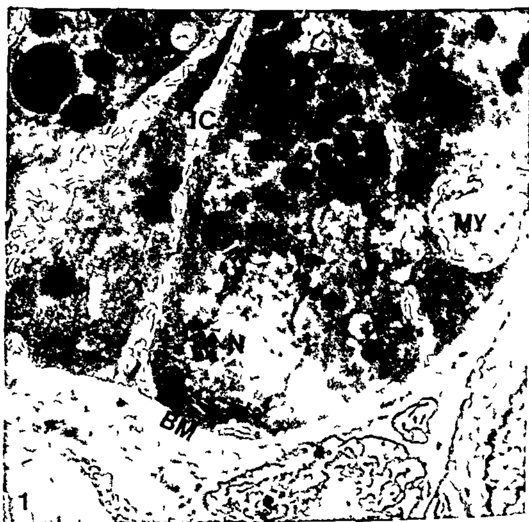


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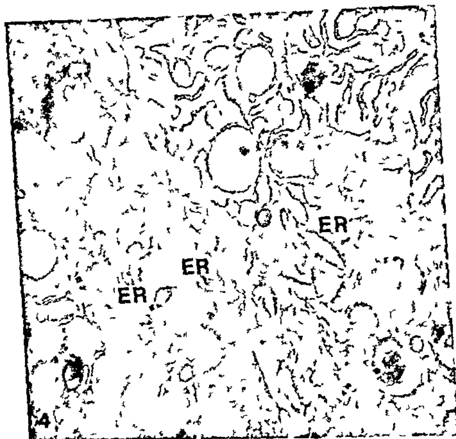


Fig 4

The degree of dilatation of the endoplasmic reticulum (ER) varies from one cell to another in the same acinus In the left cell on the figure the cisterns of the reticulum are flat or collapsed while the cell at right contains a considerably dilated rough surfaced endoplasmic reticulum Red 51 per cent from 18 500 ×

microvilli on an average 0 5 μ long and 0 1 μ broad The microvilli presented a distinctly longitudinally striated appearance (Figs 2 and 3)

The cell nuclei were all situated near the basal pole They were irregularly ovoid with the longest axis at right angles to the basement membrane Flattened nuclei similar to those observed e g in *mucinous* glandular cells were not seen The chromatin content varied usually there were one or two nucleoli

A distinct polarity was observed in the cytoplasm the dominant component in the basal portions being endoplasmic reticulum whereas the Golgi apparatus and the majority of the granules were found in the luminal portions

The endoplasmic reticulum was of the granular ribosome covered type and

could be seen that all the intercellular spaces in one terminal portion communicated whereas they were closed basally by the basement membrane and luminally by junctional complexes (Fig 2) The content of the intercellular spaces was clear and without any structure

The basal cell membrane was uniform and without any folds whereas the portion of the cells facing the lumen of the acini were provided with irregular

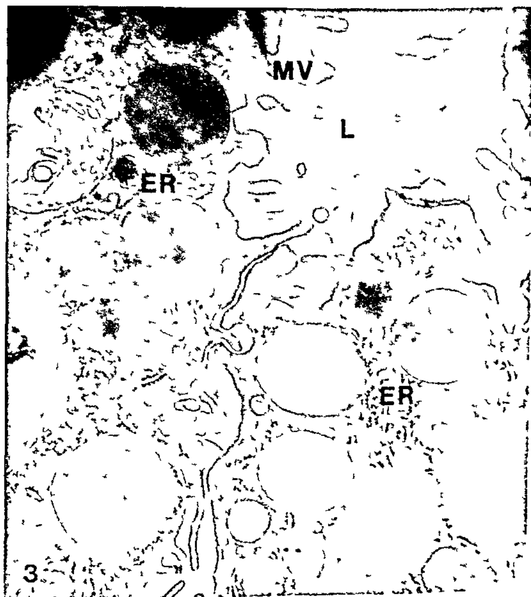


Fig 3

Dark and light granules of approximately the same size occur in the apical parts of the cells the light granules being outnumbered by the dark ones No transition between *the two types of granule is seen* L lumen MV microvillus ER endoplasmic reticulum Red 51 per cent from 42 800 ×



Fig 6

In the basal part of some of the cells one or more large irregular granules may be present They are surrounded by a single membrane and contain several lamellas embedded in homogeneous matrix Red 51 per cent from 18 500 ×

The size and density of the granules varied in all the cells They were situated mostly luminal and lateral to the nucleus Most of the granules were spherical elements of a high electron density and with a diameter of about 1 μ surrounded by one single membrane Internally the granules contained partly a homogeneous substance partly numerous large particles 50 70 Å large and of a high electron density (Figs 3 and 5) Furthermore three other types of granule were found but in much smaller numbers 1 granules of the same size and situated similarly to those described above but with a light and homogeneous content 2 small (0 2 μ) granules located in the area around the Golgi apparatus These granules which might show varying electron densities all contained a number of very dark particles 50 70 Å large similar to the larger

particularly well developed. The width of the cisterns was fairly constant in each individual cell, but varied from one cell to another (Fig 4). However it was not possible on this basis to distinguish between different types of cells; numerous transitory forms were seen. Although the preferred site of the endoplasmic reticulum was in the basal part of the cells, a few components could be found close to the luminal plasma membrane (Fig 5).

The Golgi apparatus was situated luminal to the nuclei. It was not very extensive and was composed of a few flattened cisterns and small vesicles with light content (Fig 5).

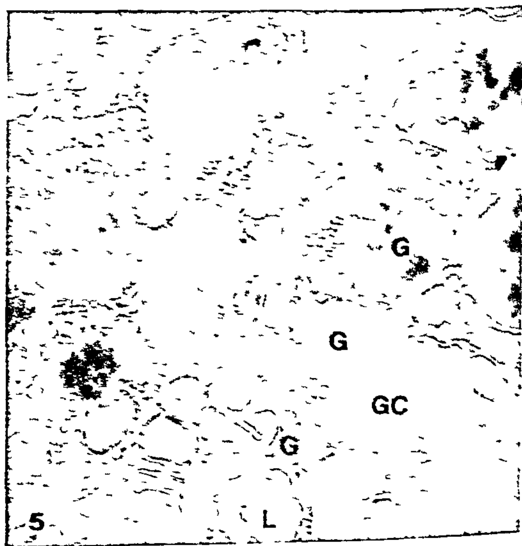


Fig 5

The Golgi complex (GC) is located in the supranuclear region in close relation with granules (G) of varying size and density. In most of the granules numerous very dense small particles are seen. L, lumen. [illegible]



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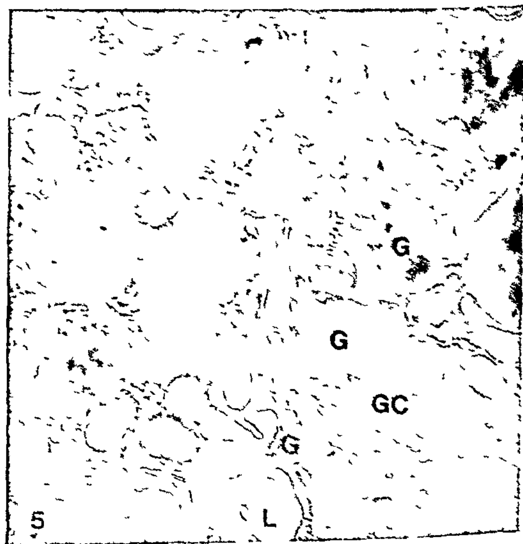


Fig 5
The Golgi complex (GC) is located in the supranuclear region in close relationship with granules (G) of varying size and density In most of the granules numerous very dense 50-70 Å particles are seen L lumen Red[illegible] per cent from 47,500 ×

ments with a pronounced polarity in which the protein synthesizing cellular organelle the ribosome covered endoplasmic reticulum is found in the basal portion whereas the Golgi apparatus and the secretory granules are located in the luminal portion In many respects the structure of the cells resembles the fine structure of the cells in other protein secreting exocrine glands the pancreas (*Palade* (1961)) the parotid gland (*Scott & Pease* (1959)) and the serous portions of the submandibular gland (*Leeson & Jacoby* (1959)) As previously mentioned the cells may show great differences as regards the density of the cytoplasm and the degree of dilatation of the endoplasmic reticulum This finding however does not justify the belief that we are faced with different types of cell with different secretory tasks More likely we are confronted with different functional capacities of the same cell type This is indicated by two conditions first that all the cells contain the same type of secretory granule in their apical portions although the number of them may vary and secondly that between the extreme types cells with a dark cytoplasm and narrow cisterns in the endoplasmic reticulum and cells with a light cytoplasm and dilated cisterns various cells are found which have transitory types of cytoplasm

The mechanism of the transmission of secretory granules from the cells into the lumen of the acini is not known Studies made on exocrine cells in the pancreas seem to show that the membrane which surrounds granules bursts and merges with the apical cellular membrane whereupon the content of the granules floats into the lumen (*Palade et al* (1962)) It is not certain that the same process occurs in the lacrimal gland since in the lumen of some of the terminal portions elements of the same size and shape as the secretory granules could be observed although their content was much lighter and the surrounding membrane seemed to be incomplete (Fig 2) These findings can be interpreted as showing that the secretory granules are expelled in an intact state from the glandular cells and that no fusion takes place between the membrane of the granules and the plasma membrane in this gland

Summary

The ultrastructure of the acini was examined in three specimens of the human lacrimal gland The acini consisted of two types of cell glandular cells and myo epithelial cells both of which were in contact with the basement membrane The glandular cells were quantitatively different as regards contents of organelles and granules but on the basis of morphological criteria it was not possible to demonstrate the presence of more than one type of glandular cell In the luminal portions of the glandular cells numerous secretory granules were found most likely originating from the Golgi apparatus The mechanism of secretion is briefly discussed



Fig 7

The myo epithelial cells are placed beneath the glandular cells close to the basement membrane (BM) The cells are interdigitating with the secreting cells by means of cytoplasmic extensions The cytoplasm is relatively poor in organelles but contains bundles of thin fibers (F) oriented parallel to the basement membrane
Red 56 per cent from 26 500 ×

granules (Fig 5) 3 The last type of granule (Fig 6) was seen in only few of the cells They were usually large (up to 7 μ) and of irregular shape located in the basal part of the cells These granules contained two components a homo geneous substance of a density corresponding to the luminal granules and membrane like structures frequently arranged in spiral shaped patterns re sembling myelin figures

Myo epithelial cells All these cells were located in the basal portions of the acini The part of the cell which faced the basement membrane had several small folds whereas otherwise the cell interdigitated with the surrounding glandular cells by means of finger shaped cytoplasmic outgrowths The cyto plasm of the myo epithelial cells contained thin filamentous structures mainly arranged at planes parallel to the basement membrane (Fig 7)

Discussion

The investigations show that the secretory cells in the acini of the human lacri mal gland are composed according to the same basic pattern cone shaped ele

ments with a pronounced polarity in which the protein synthesizing cellular organelle the ribosome covered endoplasmic reticulum is found in the basal portion whereas the Golgi apparatus and the secretory granules are located in the luminal portion In many respects the structure of the cells resembles the fine structure of the cells in other protein secreting exocrine glands the pan creas (*Palade* (1961)) the parotid gland (*Scott & Pease* (1959)) and the serous portions of the submandibular gland (*Leeson & Jacobs* (1959)) As previously mentioned the cells may show great differences as regards the density of the cytoplasm and the degree of dilatation of the endoplasmic reticulum This finding however does not justify the belief that we are faced with different types of cell with different secretory tasks More likely we are confronted with different functional capacities of the same cell type This is indicated by two conditions first that all the cells contain the same type of secretory granule in their apical portions although the number of them may vary and secondly that between the extreme types cells with a dark cytoplasm and narrow cisterns in the endoplasmic reticulum and cells with a light cytoplasm and di lated cisterns various cells are found which have transitory types of cytoplasm

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EVALUATION OF VARIOUS VASOCONSTRICTORS IN CATARACT SURGERY

BY

J S MATHUR K. S MEHRA V THAKUR and H V NEMA

As the field of operation is very limited in Cataract Surgery the value of haemostasis during operation cannot be over emphasized It is also a well established fact that any blood present on the anterior surface of the lens may make it too slippery for the forceps to hold it with perfect ease (*Stallard* 1958 *Philips* & *Foster* 1961) Commonly adrenaline is used to get quick haemostasis Recently *Mathur* & *Mathur* (1965) evaluated the role of adrenaline in cataract surgery and reported encouraging results They observed that the maximum blanching effect of the drug starting 2 3 minutes after instillation lasted for about 8 9 minutes However the drug is known to have a disadvantage in the form of rebound phenomenon (*Gartner* 1944) Adrenaline therefore can not be taken as an ideal haemostatic agent Recently Xylometazoline hydrochloride and Phenylephrine hydrochloride have been added to the list of decongestants

The present paper deals with our observations on the comparative studies on adrenaline xylometazoline hydrochloride and phenylephrine hydrochloride as haemostatic agents in cataract surgery

Material and Methods

100 cases of senile cataract whose ages ranged between 50 65 years were the subjects of this study A careful history for any bleeding disease was taken Patients with signs of hypertension diabetes or any bleeding disease were ex

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cluded Cases having active trachoma conjunctivitis or corneal vascularization were also not included in this study The cases were randomly divided into 4 groups of 25 patients each (Groups A B C and D) Group A consisted of those eyes in which Adrenaline drops 1 1000 were instilled Group B was kept on xylometazoline hydrochloride drops (0 1 %) Eyes in group C received phenylephrine hydrochloride drops (10 %) while in Group D *(control)* distilled water was dropped in the eyes Drugs in each group were instilled only once just two minutes before making the conjunctival flap

The technique of operation was the same in all the four groups A small (3 4 mm) conjunctival flap was prepared one pre incisional corneo scleral suture was placed, limbal section was made and a small peripheral pin hole iridectomy was done The amount of bleeding in these eyes was graded accordin to the criterion described earlier (*Ir asthi Mathur, Mathur & Saxena* 1964) In the present evaluation, analysis was made under only two heads viz (i) bleeding (+ and + +) & (ii) no bleeding (0) groups

Results

During cataract surgery if no haemostatic agent is used (Group D) bleeding occurs in 72 % of cases out of which 36 % is moderate to severe 68 % of cases belonging to phenylephrine hydrochloride group showed bleeding On the other hand the bleeding seen in xylometazoline hydrochloride and Adrenaline groups was 56 % and 40 % respectively (table) In other words Adrenaline xylometazoline hydrochloride and phenylephrine hydrochloride showed their haemostatic effect in 60 % 44 % and 32 % eyes respectively as compared to 28 % haemostasis recorded in the control group

Discussion

In the present study three drugs having a vasoconstrictor action have been evaluated in a small number of cataract cases It appears from the table that all the three drugs (Adrenaline xylometazoline hydrochloride and phenylephrine hydrochloride) have acted as haemostatic agents as compared to the control group Just to know whether the haemostatic effect of these drugs was a chance factor or significant the data was subjected to statistical analysis It was observed that adrenaline was responsible for checking the bleeding in 60 % of cases which is statistically significant as compared to the control group (χ = 3 98 P $<$ 0 05) Although xylometazoline hydrochloride caused haemo

Table I

Showing the haemostatic effect of various drugs during cataract surgery

Amount of bleeding	Group A Adrenaline		Group B Otrivin		Group C Drisyn		Group D Control	
	No of cases	%	No of cases	%	No of cases	%	No of cases	%
++	2	8	5	0	7	28	9	36
+	8	32	9	36	10	40	9	36
0	15	60	11	44	8	32	7	28
Total			25		25		25	

\+ – Slight bleeding
0 – No bleeding or very slight oozing
++ – Moderate or severe bleeding

stasis in 44 % of eyes it is statistically insignificant ($x^2 = 0.78$ $P > 30$) Nevertheless effect of phenylephrine hydrochloride is very insignificant.

From this analysis, therefore, one may infer that adrenaline (1 1000) is the only established haemostatic agent However it was interesting to record that the inter group comparison of groups A and B was also statistically insignificant ($x^2 = 0.72$ $P > 30$)

Summary and Conclusions

100 eyes for cataract operations were selected Four groups of 25 eyes each were made Adrenaline xylometazoline hydrochloride and phenylephrine hydrochloride drops locally were tried in groups A B and C respectively Group D served as the control

It has been observed that adrenaline reduced the incidence and the amount of bleeding in significant number of cases while xylometazoline hydrochloride and phenylephrine hydrochloride showed some haemostatic effect which was not found to be significant

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Aus der Universitats Augenklinik Halle (Saale)
(Direktor Prof Dr K E Kruger)

BEITRAG ZUR ÄTIOLOGIE DES STILLING TÜRK DUANE SYNDROMS

VON

K E KRÜGER

Zur klassischen Symptomatologie des Stilling Turk Duane Syndroms gehort bekanntlich

1 Verminderte oder aufgehobene Abduktionsfahigkeit eines Auges
2 Erweiterung der Lidspalte beim Abduktionsversuch des kranken Auges
3 Normale oder verminderte Adduktion und Konvergenzschwache
4 Lidspaltenverengerung bei Adduktion des kranken Auges (*Pseudoptosis*)
5 Retraktion des Bulbus in die Orbita oft mit gleichzeitiger vertikaler Komponente
6 Horizontale Stellunganomalien in Primarstellung (in manchen Fallen)

Die erste Beschreibung dieser Symptome erfolgte wahrscheinlich 18[illegible]5 durch *Williams* 1885 durch v *Graefe* und 1895 durch *Sinclair*

Die einschlagigen Mitteilungen durch die Autoren die dem Syndrom den Namen gaben wurden 188[illegible] von *Stilling* 1896 von *Turk* und 1905 von *Duane* publiziert Letzterer stellte 4[illegible] Falle aus der Literatur zusammen und berichtete uber [illegible] eigene Falle In der Folgezeit wurden noch zahlreiche Falle mitgeteilt Weitere Zusammenstellungen der Literatur finden sich bei *Danis Huber Duke Elder Orlowski* und Mitarb *Waardenburg Esslen* und *Papst Strampelli Ernest* und *Costenbader* u a

Neben dem klassischen Syndrom sind in den vergangenen Jahren auch atypische Krankheitsbilder beschrieben worden *Malbran* bezeichnet das atypische Syndrom bei dem aufgehobene oder stark eingeschrankte Adduktion bei Di

Auszugsweise vorgetragen auf dem II Kongress Consilium Europaeum Strabismi Studio Dedicatum in Leipzig v 27 [illegible] 1968
Eingegangen am 19 November 1969

stasis in 44% of eyes it is statistically insignificant ($x^2 = 0.78$ $P > 30$) Nevertheless effect of phenylephrine hydrochloride is very insignificant

From this analysis therefore, one may infer that adrenaline (1 1000) is the only established haemostatic agent However it was interesting to record that the inter group comparison of groups A and B was also statistically insignificant ($x = 0.72$ $P > 30$)

Summary and Conclusions

100 eyes for cataract operations were selected Four groups of 25 eyes each were made Adrenaline xylometazoline hydrochloride and phenylephrine hydrochloride *drops locally were tried in groups A B and C respectively* Group D served as the control

It has been observed that adrenaline reduced the incidence and the amount of bleeding in significant number of cases while xylometazoline hydrochloride and *phenylephrine hydrochloride showed some* haemostatic effect which was not found to be significant

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Aus der Universitäts-Augenklinik Halle (Saale)
(Direktor: Prof. Dr. K. E. Krüger)

BEITRAG ZUR ÄTIOLOGIE DES STILLING-TÜRK-DUANE-SYNDROMS

VON

K. E. KRÜGER

Zur klassischen Symptomatologie des Stilling-Türk-Duane-Syndroms gehört bekanntlich:

1. Verminderte oder aufgehobene Abduktionsfähigkeit eines Auges.
2. Erweiterung der Lidspalte beim Abduktionsversuch des kranken Auges.
3. Normale oder verminderte Adduktion und Konvergenzschwäche.
4. Lidspaltenverengerung bei Adduktion des kranken Auges (Pseudoptosis).
5. Retraktion des Bulbus in die Orbita, oft mit gleichzeitiger vertikaler Komponente.
6. Horizontale Stellunganomalien in Primärstellung (in manchen Fällen).

Die erste Beschreibung dieser Symptome erfolgte wahrscheinlich 1875 durch *Williams*, 1885 durch v. *Graefe* und 1895 durch *Sinclair*.

Die einschlägigen Mitteilungen durch die Autoren, die dem Syndrom den Namen gaben, wurden 1887 von *Stilling*, 1896 von *Türk* und 1905 von *Duane* publiziert. Letzterer stellte 47 Fälle aus der Literatur zusammen und berichtete über eigene Fälle. In der Folgezeit wurden noch zahlreiche Fälle mitgeteilt. Weitere Zusammenstellungen der Literatur finden sich bei *Danis*, *Huber*, *Duke-Elder*, *Orlowski* und Mitarb., *Waardenburg*, *Esslen* und *Papst*, *Strampelli*, *Ernest* und *Costenbader* u. a.

Neben dem klassischen Syndrom sind in den vergangenen Jahren auch atypische Krankheitsbilder beschrieben worden. *Malbran* bezeichnet das atypische Syndrom, bei dem aufgehobene oder stark eingeschränkte Adduktion bei Di

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stasis in 44 % of eyes it is statistically insignificant (χ^2 = 0 78 P > 30) Nevertheless effect of phenylephrine hydrochloride is very insignificant.

From this analysis therefore, one may infer that adrenaline (1 1000) is the only established haemostatic agent However it was interesting to record that the inter group comparison of groups A and B was also statistically insignificant (χ^2 = 0 72 P > 30)

Summary and Conclusions

100 eyes for cataract operations were selected Four groups of 25 eyes each were made Adrenaline xylometazoline hydrochloride and phenylephrine hydrochloride drops locally were tried in groups A B and C respectively Group D served as the control

It has been observed that adrenaline reduced the incidence and the amount of bleeding in significant number of cases while xylometazoline hydrochloride and phenylephrine hydrochloride showed some haemostatic effect which was not found to be significant

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wurde Auch unelastische Bander am hinteren Bulbusabschnitt oder ein ata vistischer Retractor bulbi wurden diskutiert *Lagleyze* (1913) und *Dodds* (1926) fanden dagegen die Mm recti normal Es muss aber betont werden dass von vielen Untersuchern keine anatomischen Befunde mitgeteilt oder keine histo logischen Untersuchungen durchgefuhrt wurden

Mit zunehmender Einfuhrung der Elektromyografie in die Augenheilkunde hat man als Ursache fur das Syndrom innervatorische Anomalien der Augen muskeln in den Vordergrund geruckt So beschrieben *Breinin* *Papst* und *Essl n* *Huber* und Mitarb Dell *Aquila* und *Molinari* *Sato* u a *Orlowski* und Mitarb *Blodi* und Mitarb *eine Zunahme der elektrischen* Aktivitat bei Adduktion im M rect ext bei gleichzeitiger normaler Aktivitatszunahme im Musc rect in ternus also eine Storung der reziproken Innervation Solche paradoxen Inner vationen wurden auch zwischen anderen Muskeln gefunden z B zwischen dem M rect lateralis und einem vertikalen M rect Wahrend *Breinin* seinen Be fund als Dehnungseffekt deutete – im ubrigen fand er die paradoxe Innerva tion nur bei einer bestimmten Nadellage in dem untersuchten M rect lat – nahmen die meisten Autoren an dass die paradoxe Innervation eine Folge supranuklearer Innervationsstorungen sei Wahrend *Papst und Esslen* auf Grund ihrer elektromyografischen Befunde glauben eine periphere Innervationssto rung ausschliessen zu konnen sehen *Huber* und Mitarb aus theoretischen Er wagungen eine periphere Lokalisation als unwahrscheinlich an

Eigene Beobachtungen

Eigene Beobachtungen von insgesamt 8 Patienten mit Stilling Turk Duane Syndrom teilten wir 1963 und 1964 *mit* denen wir in der Folgezeit noch 10 hinzufugten Bei diesen Fallen unter denen sich einseitige und doppelseitige typische und atypische Syndrome fanden konnten neben der Erhebung der ublichen klinischen Befunde auch mehrmals bei operativen Eingriffen ge wonnene Muskelstuckchen des M rect lat histologisch untersucht werden Ausserdem konnten bei mehreren Patienten elektromyografische Untersuch ungen der ausseren Augenmuskeln durchgefuhrt *werden* ** *(Tabelle I)*

Dabei wurden in einigen Fallen elektromyografische Befunde erhoben ahn lich wie sie von *Papst* und *Esslen* *Huber* und Mitarb *Orlowski* und Mitarb u a bei den von ihnen beobachteten Retraktionssyndromen gefunden wurden

In Zusammenarbeit mit Herrn Oberarzt Glatzel und Herrn Dipl Phys Tietze der Nervenklinik der Martin Luther Universitat Halle (Saale) Direktor Prof Dr Rennert)

Elektromyograph der DISA Kopenhagen

vergenzstellung des betroffenen Auges besteht als Variante II und als Variante III jene Falle bei denen die Motilitätseinschrankungen in der Vertikalen vorhanden sind

Beim Stilling Türk Duane Syndrom ist in den meisten Fallen das linke Auge betroffen seltener das rechte Auge Noch seltener wird es bilateral beobachtet *(Alexander)* Das weibliche Geschlecht ist haufiger betroffen (3 2) Neben den genannten Symptomen konnen am Auge zahlreiche andere Begleitsymptome auftreten Keratokonus Mikrophthalmus Mikrokornea Reste der Pupillarmembran Heterochromie der Iris kongenitale Katarakt tapetoretinale Degeneration Papilla leporina Netzhautkolobome Optikusatrophie Hyperopie Nystagmus subkonjunktivale Fibrome Tiefstand der Lidspalte Distichiasis Ptosis Retraktion des Oberlides u a Im Gesicht kommt einseitige Facialisparese und ausgepragte Asymmetrie vor

Weitere somatische Begleitsymptome sind Zahnanomalien Halsrippe und Klippel Feil Syndrom zusammen als Zerviko okulo Akustikus Syndrom bezeichnet (Wildervanck Waardenburg Franceschetti - Klein Syndrom) Es gehort zum Dysmorphie und Dysrhaphie Syndrom *(Waardenburg)*

Das Syndrom tritt immer kongenital auf auch wenn es oft erst spater von den Eltern bemerkt wird Neben dem sporadischen Auftreten des Syndroms ist es in mehreren Fallen auch als hereditares Leiden beschrieben worden zuletzt von *Blodi* und *van Allen* *Kambayashi* und Mitarb, *Khodahoust* und *v Noorden* u a Der Vererbungsmodus soll in den meisten Sippen autosomal dominant mit inkompletter Penetranz sein

Es kann als sicher angesehen werden dass es sich um eine embryonale Entwicklungsstorung handelt und demgegenuber geburtstraumtischen *(Gallus Gifford)* und postnatalen krankheitsbedingten Lasionen wohl kaum eine Bedeutung zukommt Damit ist jedoch die wirkliche Natur weder der Retraktionserscheinung noch der ganzen Motilitatsstorung geklart

Der Mechanismus der Motilitatsstorung hat vielmehr sehr verschiedene Erklarungen gefunden die sich meistens auf anatomische Befunde stutzen So beschrieb schon *Turl* den Musc rect lat als unelastisches Band Eine Zunahme fibrosen Gewebes zwischen den Muskelfasern oder in seiner Aponeurose fand *Mayou* (1935) Als Ursache fur solche Veranderungen wurden Entwicklungsanomalie infolge Kernaplasie oder Blutungen in die Muskelscheide angenommen *(Gallus)* Eine anomale hintere Insertion des Musc rect med soll wie ein Retractor bulbi wirken konnen *(Axenfeld* und *Schurenberg Mayou)* *Bahr* (1896) beobachtete eine Spaltung des M rect med in zwei Portionen von denen die eine 12 mm hinter dem Limbus die andere noch weiter ruckwarts inserierte Auch *Salus* (1934) *Bielschowski* (1939) *Apple* (1939) u a machten solche Beobachtungen wahrend *Cappellaro* und *Gundersen* und *Zeavin* Verwachsungen zwischen Orbita und M rect med mit seinen Fascien fanden nach deren Durchtrennung eine wesentliche Motilitatsverbesserung gefunden

Die Verengerung der Lidspalte bei Adduktion wird auch im Schrifttum auf verschiedene Ursachen zuruckgefuhrt Bei unserem Patienten mit dem ausgepragten paradoxen Innervationsmuster verengte sich die Lidspalte bei Adduktion in typischer Weise (Pseudoptosis) Der Augapfel wurde gleichzeitig so tief in die Orbita gezogen dass die Lider dem Bulbus nicht mehr anlagen und klaffend im freien Raum standen Auch wenn wir bei diesem Patienten den M levator palp nicht ableiteten war dieser Befund der Lidspaltenverengerung zwanglos mechanisch durch die Retraktion des Bulbus zu erklaren Bei diesem Patienten war in Anasthesie die passive Beweglichkeit des *betroffenen Auges* nach aussen frei und nach nasal eingeschrankt Wenn man versuchte den Bulbus in diese Richtung weiter zu rotieren trat Enophthalmus ein als Aquivalent der Retraktion bei aktiver Bewegung

Diskussion

Aus den zahlreichen Mitteilungen und aus den von uns erhobenen Befunden ergibt sich dass paradoxe Innervationsverhaltnisse in den *verschiedensten Kombinationen* im Augenmuskelnervenbereich auftreten und elektromyografisch nachweisbar sind Man kann aber nach meiner Ansicht die Retraktion des Augapfels bei Adduktion – das Leitsymptom des ganzen Syndroms – nicht auf die paradoxen Innervationsverhaltnisse zuruckfuhren bevor man nicht durch den Duktionstest eine passive Bewegungseinschrankung und damit strukturelle Veranderungen im Muskel Fascien Apparat ausgeschlossen hat Daruber fehlen aber *in vielen* Publikationen die Angaben

Wenn man neben der Einschrankung der passiven Beweglichkeit auch noch pathologische Veranderungen in den betroffenen Muskeln *findet* erscheint es geradezu unvereinbar die Retraktion *auf die* pathologischen Innervationsverhaltnisse zuruckfuhren *zu wollen* Bei der Diskussion dieser Frage durfen auch nicht die Befunde der Untersuchungen *vor* der E M G Ära unberucksichtigt bleiben z B von *Matteucci* (1946) der eine histologische Untersuchung durchfuhren konnte und Hypoplasie des Kerngebietes des N abd und seiner Fasern und fibrotische Veranderungen im M rect lat und Hypertrophie im M rect med gefunden hatte

Danach kann festbestellt werden dass die in *sehr* vielen Fallen im E M G nachweisbare paradoxe Innervation fur die Retraktion des Bulbus nur zwanglos verantwortlich gemacht werden kann wenn die in Anasthesie geprufte Motilitat regelrecht ist Ich habe keinen Fall beobachtet fur den dies zugetroffen hatte Bei den von *Huber* und Mitarb beschriebenen Fallen soll die paradoxe Innervation einerseits die Ursache d r Retraktion des Augapfels beim Duane I Typ sein andererseits aber die Erscheinung der Adduktionslahmung beim

Tabelle I
Verteilung der 18 Fälle mit Retraktions-Syndrom

weiblich		*männlich*
11		7
links	*rechts*	*bds*
14	2	2
	mit Strabismus	
convergens		*divergens*
6		1

Mehr oder weniger stark ausgeprägte paradoxe Innervationsmuster an Muskelgruppen die normalerweise dem Gesetz der reziproken Innervation unterliegen oder nicht als Synergisten wirken Auf die kasuistische Darstellung sämtlicher Befunde wird bewusst verzichtet da sie keine in wesentlichen Punkten unterschiedlichen Ergebnisse erbrachten und es uns hauptsächlich auf die Befunde des E M G ankommt die auch eine andere mir richtiger erscheinende Interpretation zulassen

Da die Retraktion des Augapfels seit der E M G Ära auf die paradoxen Innervationserscheinungen zurückgeführt wird haben auch wir besonders auf diese Beziehungen zwischen diesen beiden Symptomen geachtet Die Retraktion des Bulbus war nicht in jenem von uns beobachteten Falle am stärksten in dem wir das dichteste Interferenzmuster des M rect lat bei Adduktion fanden sondern bei einem Patienten bei dem bei der Adduktion vom M rect lat zwar noch Potentiale abgeleitet werden konnten diese aber etwa nur die gleiche Dichte wie bei der Primärstellung und bei der Abduktion zeigten Solche E M G Befunde wurden auch von *Blodi* und *van Allen* erhoben Diese Ergebnisse lassen die paradoxe Innervation als alleinige Ursache für die Retraktion fraglich erscheinen

Im Zusammenhang mit dieser Feststellung sei noch darauf hingewiesen dass wir bei mehreren Probanden einer Familie mit hereditärer kongenitaler Ophthalmoplegie elektromyografisch auch paradoxe Innervationsverhältnisse nachweisen konnten Sie hatten gleichzeitig – unterschiedlich stark ausgeprägte – Einschränkungen der passiven Motilität und zeigten damit Übergänge zum Strabismus fixus aber auch zum sog Substitutionsphänomen

Die histologische Untersuchung exzidierter Muskelstücke aus dem M rect lateralis von verschiedenen Patienten mit Retraktionssyndrom und Schielstellung des betroffenen Auges ergab degenerative Veränderungen der Muskulatur mit Vermehrung fibrotischen Gewebes

gleichgeordnete vielleicht auch voneinander abhängige Anomalien und als Folgen früher embryonaler Entwicklungsanomalien anzusehen die wahr scheinlich auf Grund der bekannten Embryonalentwicklungsvorgänge schon im 7 bis 12 mm Stadium abgelaufen sind

Diese embryonale Entwichlungsstörung kann eine hereditäre Grundlage haben andererseits auch sporadisch auftreten

Die okulare und somatische Begleitsymptomatik stellt das Stilling Türk Duane Syndrom in einen grösseren Rahmen der Missbildungsforschung worauf schon *Danis* hingewiesen hat Insbesondere sind Beziehungen zum Status dysrhaphicus hervorgehoben worden

Da man Retractio bulbi und paradoxe Innervationsanomalien auch bei anderen Motilitätsstörungen als den Stilling Türk Duane Syndromen findet lässt sich zwanglos eine Skala aufstellen von den geringsten kongenitalen Motilitätsstörungen wie sie z B in Stammbaumen von Patienten mit hereditärem Stilling Türk Duane Syndrom gefunden wurden bis zu den schwersten Formen wie wir sie z B beschrieben haben *(Krüger* und *Friedrich)* Was bisher nicht geklärt werden kann ist die deutliche Bevorzugung des linken Auges beim Stilling Türk Duane Syndrom Es liegt nahe dass in dieser Beziehung besondere entwicklungsmechanische Faktoren eine Rolle spielen

ZUSAMMENFASSUNG

Nach einem geschichtlichen Überblick wird auf die in der Literatur *angeführten Deutungen des Stilling* Türk Duane Syndrom *eingegangen* Auf Grund der bisher mitgeteilten wichtigsten und bei 18 eigenen Fällen erhobenen Befunde wird auf die zur Retraktion des Augapfels *führenden* Möglichkeiten auf die *Lokalisation der Schädigung* und ursächliche Faktoren des Syndroms hingewiesen

Es kann nicht als bewiesen angesehen werden dass die Retraktion des Augapfels *durch* die im L M G manchmal nachweisbare *paradoxe Innervation* hervorgerufen wird und diese Innervationsanomalie einen supranuklearen Sitz haben *muss Vielmehr werden die* Fakten hervorgehoben die für eine periphere Lokalisation *sprechen*

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Duane II Typ erklären Mir scheint diese Interpretation ohne genaue Prüfung der passiven Beweglichkeit nicht gerechtfertigt zu sein Ähnliches gilt für die Auslegung der E M G Befunde von *Blodi* und *van Allen* die bei ihren Fällen 1 und 2 die Retraktion bei der Adduktion darauf zurückführen dass der M rect internus bei allen Blickrichtungen die gleiche elektrische Aktivität zeigt, der M rect lat dagegen normal innerviert wird Beim 2 Fall bleibt ausserdem die Frage offen wie überhaupt die Adduktion möglich war bei fast völligem Fehlen eines Innervationsmusters Es könnte ein technischer Fehler vorgelegen haben Diese Fälle unterstützen vielmehr nur meine Ansicht dass die Retraktion des Bulbus wohl nur in seltenen Fällen wirklich Folge von Innervations Anomalien ist sondern vorwiegend durch strukturelle Veränderungen hervor gerufen wird

Nun zur Frage ob die paradoxe Innervation ein peripheres nukleares oder supranukleares Substrat hat Auch hier dürfen die Befunde früherer Autoren nicht ausser Acht gelassen werden *Hoyt* und *Nachtigaller* haben sie zusammengestellt und eigene Befunde hinzugefügt aus denen hervorgeht dass die Annahme einer supranuklearen Innervationsstörung kaum bewiesen ist und viel wahrscheinlicher eine Innervation des M rect lat durch Fasern des Nervus oculomotorius ist Den Ausführungen von *Hoyt* und *Nachtigäller* schliesse ich mich voll an Darüber hinaus muss man daran denken dass es solche peripheren kongenitalen Fehlinnervationen vom N oculomotorius möglicherweise auch für den M obl superior gibt z B könnte das Sehnenscheidensyndrom von *Brown* auf diese Weise bedingt sein denn bei der operativen Intervention eines solchen Falles konnte ich keine Sehnenscheidenveränderungen feststellen Leider konnte bei diesem Fall kein E M G des M obliquus sup und anderer Muskeln geschrieben werden

Weiterhin ist die Frage zu klären wie die peripher anatomischen Muskelbefunde einzuschätzen sind *Orlowski* und Mitarb betrachten sie als sekundär und führen dafür *Waardenburg* an *Waardenburg* stellt die Frage ob die normale autochthone Entwicklung der Muskeln für ihre Kontinuität neurotrophischer Verbindungen bedarf und hält auf Grund eines von *Bielschowski* beschriebenen Falles die Möglichkeit offen Es ist zwar erwiesen dass die Muskulatur zu ihrer Entwicklung der Verbindung mit den nervösen Zentralorganen durch die peripheren Nerven nicht bedarf *(Schaper Harrison Goldstein)* dass sie aber besonders leicht zur Degeneration neigt Hierauf hat kürzlich *Duallas* erneut hingewiesen Für die kongenitalen Ophthalmoplegien einschliesslich des Duane-Syndroms ist m E auch die Annahme einer primären Fehlentwicklung bzw Fehldifferenzierung möglich andererseits aber auch eine sekundäre Degeneration von Muskelgewebe nicht auszuschliessen

Zusammenfassend ist festzustellen dass die Retraktion des Bulbus nach unserer Ansicht Folge struktureller Anomalien des Muskel Fascienapparates ist Diese und die elektromyografisch festgestellten Innervationsanomalien sind

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The pigmentary glaucoma usually displays the following clinical signs

1 Pigment deposits in a vertical line on the central corneal endothelium (Krukenberg spindle)

2 Pigmentation of the angle in its entire circumference the zonulae and the lens equator

3 Peripheral iridodonesis

4 Incomplete development of the angle with persisting mesoderm (Malbran) often covered by pigmentation

5 Progressive atrophy of the pigment epithelium of the iris [1, 2, 10, 14, 18]

6 Normal or increased depth of the anterior chamber

7 Myopia often combined with astigmatism

8 Ocular hypertension with onset between 20 and 50 years

The pathogenesis of pigmentary glaucoma is not clear and its nosological entity questioned by several authors Sugar[18] suggested that the progressive migration of pigment from the iris epithelium would eventually block the trabecular pores and obstruct the outflow channels This theory is attractive but cannot be applied to all cases for the following reasons

1 Glaucoma develops only in a certain percent of eyes with heavy pigmentation of the angles and Krukenberg spindles The rate of glaucoma is only 5 % according to Bick[1] in a material of 123 female patients with Krukenberg spindles but 43 5 % according to Scheie and Fleischhauer[16]

2 Pigment granules are not with certainty blocking the pores of the trabecular meshwork but are found mostly in the corneoscleral trabecular proper as well as inside the corneal endothelial cells[6, 7]

3 The Krukenberg spindle and the distribution of pigment in the angles does not correspond to that of other secondary deposits (diabetic or uveitic) as described by François[4] The uniform pigmentation of the angle circumference and the line of Schwalbe instead suggests a congenital origin

The following case reports emphasize the dysgenetic findings in the anterior chamber and especially in the architecture of the angle

Case Report

CASE I Male age 48 Examined in December 1961 because of loss of nasal field of the left eye

Family history negative

Ocular anamnesis Myopia known since school age Sporadic headache but never haloes

O D V A 0 3 (– 5 75 sph) *Tension* 8 *mm* Schiotz Cornea clear except for a luster of fine pigmented points on the central endothelium No myopic fundus changes Glaucomatous cupping of the disc

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GONIODYSGENESIS AND PIGMENTARY GLAUCOMA

BY

TORD JERNDAL

The pigmentary glaucoma was first described as a clinical entity by Sugar and Barbour in 1949[17] and although rare it has attracted considerable and growing interest In the classification of glaucomas it was first referred to a group of its own since it differed from both the open and the narrow angle glaucomas François[5] has called it the only true juvenile glaucoma but this characterization is misleading since the onset of the disease is not exclusively found in juvenile patients

In 1957 Malbran[1] published 7 case reports on pigmentary glaucoma with gonioscopic findings that strongly suggested a relation to the congenital glaucomas According to *Malbran* (1968)[13] the diminished outflow is caused by dysgenesis of the angle structures rather than obstruction of the trabecular pores by pigment granules The gonioscopic findings in support of the dysgenetic theory were

1 High insertion of the iris with a wide rounded angle

2 A cellophane film and remains of fetal mesoderm in the angle

3 Combination with other ocular malformations viz megalocornea Other authors have added hydrophthalmus ectopia and coloboma of the lens and cranio facial dysostosis[13]

4 Juvenile or presenile onset

In this context it is also interesting to recall that Krukenberg who in 1899 gave the first description of a pigmentary glaucoma attributed the corneal pigment to "inborn melanosis[8]

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At 5 6 o clock two black quadrangular flakes were seen on the membrane In several places vascular loops were perforating the membrane and intermingling with its tissue

Perimetry Double Bjerrum scotoma with a break through in the upper nasal quadrant

CASE 2 Identical twin daughter of case 1 age 24

No ocular complaints Both eyes Emmetropia normal tension and no abnormal pigmentation or depigmentation The only anomalous findings concerned the iris stroma and chamber angle The stroma in the sphincter area was very thin in contrast to the well developed collarette Discrete inferior coloboma of the iris *stroma* bilaterally

Gonioscopy Transparent uveal meshwork with superimposed gracile iris processes of normal appearance except for in the colobomatous area Here the line of Schwalbe was thickened and pearly white From the extreme iris base a few cords free from the uveal meshwork reached the line of Schwalbe a finding that conspicuously differed from the flat and slender iris processes outside the coloboma In the angle at 7 o clock a tortuous vessel with an oblique anomalous course at the iris base

CASE 3 Identical twin sister of case 2

Iris morphology and gonioscopy findings exactly a copy of those of case 2

Comment The congenital anomalies of the chamber angle varied from the heavily pigmented mesodermal membrane of the father to a few mesodermal cords in the colobomas of the twins Atrophy of the iris stroma was present in all three but varied in distribution The bilateral incomplete colobomas of the twins give indirect support to the supposedly dysgenetic nature of the pigmentary glaucoma of the father

CASE 4 Waiter age 63 Attended the clinic in 1966 because of hazy vision due to glaucoma

Family history negative

General anamnesis High blood pressure known since 1956 Left hemiparesis since 1959

Ocular anamnesis Glaucoma was discovered in 1966 and controlled with topic pilocarpine and epinephrine Normal vision but glaucomatous cupping and field defects of both eyes *Poorly controlled* tension led to hospitalization in October 1968

O D V A 1 0 (-1 00 sph) Tension 27 33 mm Schiotz Typical *Krukenberg spindle* No flare or pigment floaters Increased depth of anterior chamber At the iris periphery at [illegible] o clock a lacunar *depression with a heavily* pigmented naevus No pigment atrophy of the iris Marginal cupping of the disc with nasal displacement of vessels

Gonioscopy Wide angle Moderate pigmentary deposits in front of a poorly developed line of Schwalbe *From* the iris base a thick uveal meshwork with a lace like surface filled the *recess almost* to the line of Schwalbe The canal of Schlemm the scleral spur and the *ciliary* band were covered and could *not* be *identified* At 6 o clock corresponding to the mentioned peripheral *iris naevus* the iris base was slightly depressed and the uveal membrane thinned *allowing inspection* of the scleral spur and the anterior fringe of the ciliary band In *the upper half* of the angle the uveal meshwork was less compact over the *trabecular band* Here a circumferentially oriented [illegible] brown string overlying the uveal meshwork *followed* the approximate course of the canal of Schlemm

O S V A 0 1 (1 00 sph) Tension [illegible] mm Schiotz Krukenberg spindle in the meridian Deeply excavated optic *disc*

O S V A 0 4 (−6 00 sph) Tension 47 mm Schiotz Denser corneal pigmentation than in O D and pronounced glaucomatous cupping of the disc

Gonioscopy O D = O S Patchy atrophy of the iris base The ring of Schwalbe strongly developed A thick and richly pigmented meshwork completely bridging the angle

Perimetry O D Enlarged blind spot O S Pronounced field defects with central and lower temporal rests

Tension variations without therapy (3 days) O D 26 40 mm O S 33 50 mm Schiotz

With 2% pilocarpine instillations three times daily and 1% pilocarpine ointment at night tension was controlled In September 1963 a rise of tension and a progressive reduction of the visual field of the left eye demanded additional treatment with azetazolamide (Diamox®) 125 mg three times a day Control of tension was not obtained so in June 1964 an iridencleisis was performed in the left eye without complications. Later on also the right eye showed poorly controlled tension and a progressive reduction of the visual field and an iridencleisis was performed in this eye in September 1963

Postoperative hypotension in the right eye and normal tension in the left eye without additional treatment

Findings in July 1968 at a routine check up

O D V A 0 5 (−6 00 sph −0 5 cyl × 90°) Tension 4 mm with applanation tonometry Corneal diameter 12 25 mm Cornea clear except for a typical Krukenberg spindle of moderate density No flare or pigment floaters Iridencleisis with large subconjunctival bleb Iris stroma atrophic and greenish blue with an irregularly prominent collarette of pale yellow colour Very few pigment granules of the iris surface Slight nuclear cataract Vitreous moderately cloudy Optic disc pale with almost marginal cupping No myopic fundus changes Biomicroscopy with retroillumination failed to reveal any atrophy of the pigment epithelium of the iris

Gonioscopy Wide rounded angle From the iris base a greyish brown membrane covered the recess and inserted into the trabecular band Intensely pigmented rim along the site of Schlemm s canal The canal itself the scleral spur and the ciliary band were concealed by the membrane and could not be identified

Perimetry Enlarged superior Bjerrum scotoma

O S V A 0 1 (−7 00 sph −0 50 cyl × 90°) Tension 10 mm with applanation tonometry Corneal diameter 12 25 mm Krukenberg spindle slightly denser marked than in the right eye Large peripheral iridectomy after surgery Marked subconjunctival filtration bleb Atrophic iris stroma with intact pigment epithelium and vitreous opacities as in the right eye Optic disc deeply cupped with a slightly undermined nasal border Central fundus without degenerative changes but in front of the equator at 6 o clock a pearshaped vertically oriented choroidal defect (coloboma?) Separated by normal retina from this defect was an area of small rounded pigmented degenerations at the periphery at 4 5 o clock

Gonioscopy Peripheral iridodonesis Wide rounded angle The iris surface from the collarette to the base was covered by a greyish yellow membrane (remnants of the pupillary membrane) At the angle this membrane left the iris proper to insert between the scleral spur and the line of Schwalbe thus forming a rounded inner wall of the angle Heavy brownish black pigmentation as a distinct band following the site of Schlemm s canal and a less pigmented line situated in front of the line of Schwalbe

formations Case 4 also lacked atrophy of the iris pigment epithelium The appearance of the Krukenberg spindles indicated a possible congenital origin

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Gonioscopy Identical with the right eye but the discrete cleft in the uveal meshwork was located at 6 30 exactly in the direction of the oblique Krukenberg spindle

Comment A typical pigmentary glaucoma with moderate pigmentation of the angles The typical mesodermal remnants in the angles and the lack of pigment atrophy of the *iris made it a* most probable case of late congenital glaucoma

Conclusion

Case 1 *showed* heavy pigment deposits in the angles and typical Krukenberg spindles but *completely* lacked any atrophy of the pigment epithelium of the iris on retroillumination why the pigmentation could not possibly be of iridial origin By gonioscopy it was demonstrated that a thick membrane of the uveal meshwork obstructed the filtering portion of the angle analogous to the picture found in congenital glaucoma The twin daughters of the patient displayed colobomas of the iris *stroma* with discrete angle malformations in the corresponding sectors These findings of goniodysgenesis are interpreted as hereditary developmental defects They are too minute to produce glaucoma in the twins but are extensive in the father where they cause defenite reduction of outflow and eventually glaucoma

Case 4 did not show any pigment atrophy of the iris and only moderate pigmentation in the angles in spite of bilateral Krukenberg spindles Gonioscopy *demonstrated* a felty uveal meshwork that seemed to give an anterior insertion of the iris a finding that closely resembles the picture often seen in congenital glaucoma The iris base was slightly depressed at 6 o clock in the right eye and at 6 30 in the left eye thus forming a discrete incomplete coloboma of a type similar to that described by Sampaolesi [15] It was interesting to note that the axis of the Krukenberg spindle of each eye was oriented towards the coloboma This finding suggests that the Krukenberg spindle might be a congenital phenomenon or in Krukenberg s own words an inborn melanosis

Summary

Recently suggestions have been made that developmental defects in the anterior chamber angle are of primary importance in pigmentary glaucoma These views are verified by reporting two cases of pigmentary glaucoma with obvious goniodysgenesis Case 1 displayed all characteristics of the pigmentary glaucoma except atrophy of the pigment epithelium of the iris The identical twin daughters of case 1 although non glaucomatous also displayed discrete signs of dysgenesis of the anterior chamber indicating a hereditary character of the mal

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From the Department of Medical Microbiology
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DISTRIBUTION OF TRITIATED TETRACYCLINE IN THE RABBIT EYE

BY

L SALMINEN H JARVINEN and P TOIVANEN

Introduction

The enhancement by infection of benzylpenicillin penetration in the rabbit eye was demonstrated in a previous communication (*Salminen et al* 1969) Most striking was the effect of infection in the aqueous humor but higher concentrations than normal were also found in other parts of the infected eye excluding the vitreous body The effect is due partly to the hyperemia but changes must also be involved in the tissue permeability which facilitate the penetration of drugs bound to serum proteins To further elucidate this phenomenon we found it important to study the ocular distribution of some other antibiotic which is not bound by serum proteins to the same extent as benzylpenicillin There are marked differences in this respect between various penicillins (*Scholtan* 1968) but for the present labelled derivatives other than benzylpenicillin are not available We have chosen tetracycline of which 20 to 30 per cent is known to be bound to serum (*Kunin et al* 1959 *Scholtan & Schmid* 1963) the corresponding value for benzylpenicillin is twice as high

Tetracycline has been claimed to be superior to chlor and oxytetracycline in its penetrability in the aqueous humor from the plasma (*Abraham & Burnett*

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1955) but after the intravenous administration of a large dose 50 mg/kg therapeutic concentrations of oxytetracycline have been observed in the rabbit aqueous humor cornea conjunctiva sclera and iris while in the vitreous body chorioretina and lens no detectable amounts were found (*Cannon et al* 1952) Parenteral injection of 20 to 30 mg/kg of tetracycline resulted in measurable concentrations in the rabbit aqueous but not in the vitreous body (*Furgiuele* 1961) chlortetracycline could not be found even in the aqueous (*Douvas et al* 1951) In other studies chlortetracycline as well as demethylchlortetracycline have however been detected in the rabbit aqueous humor after oral administration and chlortetracycline also in other parts of the rabbit eye (*Bleeker & Maas* 1955 *Knothe* 1959) Antibiotic concentrations in all these studies have been determined using microbiological methods which cannot be applied to infected specimens We will here describe the distribution of tritiated tetracycline in the rabbit eye infected with staphylococci In principle the results resemble those obtained with tritiated benzylpenicillin but certain differences are to be found

Material and Methods

Animals Twenty eight rabbits from both sexes weighing 2 3 to 2 7 kg were used as the test animals

Induction of infection A tetracycline sensitive *Staphylococcus aureus* strain ATCC 6538P was used The left eye of each rabbit was infected by inserting staphylococci into the vitreous body through the sclera with a thin needle under local Novesin® anesthesia Vitreous abscess or panophthalmitis developed in the infected eyes within 18 hours

Tetracycline injection Tetracycline 7 T monohydrochloride (specific activity 144 mC mM The Radiochemical Centre Amersham England) and nonradioactive tetracycline monohydrochloride (kindly supplied by Leiras Manufacturers Turku Finland) were used Twenty five rabbits were injected subcutaneously with 2 5 ml of an aqueous solution containing 25 mg of tetracycline hydrochloride and an amount of 0 1 mC (222 × 10⁶ dpm) of the labelled material The dosage is equal to 10 mg 0 04 mC/89 × 10⁶ dpm/kg of the body weight 10 000 dpm corresponds to 1 1 μg of the injected drug Tetracycline was injected 18 hours after induction of the infection A control group which was not injected with tetracycline consisted of three rabbits

Preparation and counting of samples was carried out mainly as described previously (*Salminen et al* 1969) Specimens from the aqueous humor cornea lens vitreous humor and iris of both eyes and from the brain heart blood

liver lung and renal cortex were prepared as earlier The lens was prepared as a whole with the capsule and split into two halfs of which the other was used In addition separate samples were taken from the chorioidea sclera retina and ciliary body of both eyes A triangular piece was prepared from the sclera not very near the richly vascularized limbus Retina samples consisting of the anterior retina were always contaminated by the vitreous humor because of the close adherence to it The specimens weighing 10 or 200 mg were digested with perchloric acid and hydrogen peroxide and counted using a liquid scintillation spectrometer The mean counts for the tissues of the control animals were used as background values

Statistics The Student s *t*-test was employed in comparing the means

Results

The radioactivity in different tissues of rabbits with staphylococcal infection in the left eye is presented in Figs 1 3 The renal cortex is excluded in the figures its radioactivity was five to twelve times higher than the corresponding

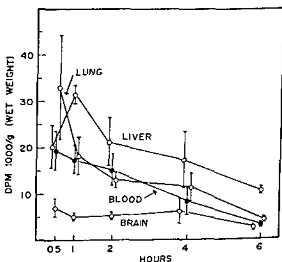


Fig 1

Radioactivity in the rabbit lung liver blood and brain during six hours after a subcutaneous injection of 0 1 mC/222 × 10^6 dpm of tritiated tetracycline hydrochloride with 25 mg of the unlabelled tetracycline 10 000 dpm corresponds to 1 1 μg Each point is the mean value of five rabbits the vertical bars are standard errors of the values

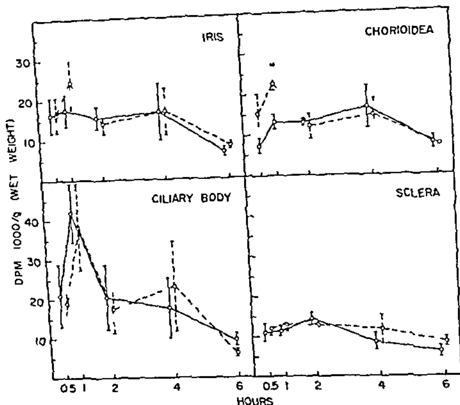


Fig °

Rad oactivity in the vascularized tissues of the noninfected eyes (solid line) and of the eyes with staphylococcal infection (broken line) of the same rabbits as in Fig 1 Each po nt is the *mean value* of five (in a few cases four) eyes the vertical bars are standard errors of the values Asterisks refer to the level of significance when the noninfected and infected eyes are *compared* * * $P < 0.001$ $P < 0.01$ and * $P < 0.05$

blood level The concentrations found in the ciliary body iris chorioidea and sclera are the highest in the eye and are approximately equal to those of the blood at the same time the radioactivity of the ciliary body one hour after the tetracycline injection is even greater than in the blood The lowest concentra tions are in the vitreous body and retina while the aqueous humor cornea and lens show intermediate values of about the same level as the concentrations in the brain The infected eye has on some occasions significantly greater radio activity than the healthy one in the aqueous humor cornea retina and chori oidea

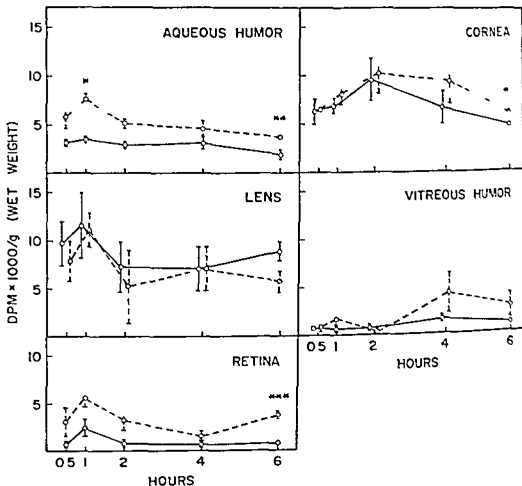


Fig 3

Radioactivity in the unvascularized compartments and in the retina of the same eyes as in Fig 2 See the legend to Fig 2 for explanation

Discussion

The differences observed in this work between the radioactivity of the infected eye and the healthy one are not as definite as those found in the study on benzylpenicillin (*Salminen et al* 1969) The aqueous humor of the infected eye had up to three times the normal penicillin concentration The time between the bacterial inoculation and the drug injection was in the present work 18 *hours* instead of the 24 hours interval used earlier Macroscopically this resulted in no difference in the infection but may influence on the tissue hyperemia However the current findings are also consistent with the view that *protein* bound benzylpenicillin contributes to the high penicillin concentrations in the aqueous humor Changes in the blood aqueous barrier cannot enhance the penetration of

the less bound tetracycline to the same extent Definite conclusions are not possible on the basis of these results further comparisons including quantitation of proteins in the aqueous and of drugs bound to them are needed

Another difference between tetracycline and benzylpenicillin lies in the concentrations found in the lens and vitreous body In the study on benzylpenicillin both showed about equal levels but tetracycline concentrations are clearly higher in the lens than in the vitreous The high radioactivity in the lens is surprising since no contamination is possible Samples from the aqueous were collected from the anterior chamber and greater concentrations in the posterior chamber are possible This and the high concentration in the ciliary body probably result in the rapid diffusion of the free tetracycline in the lens The radioactivity found in the vitreous body represents that in the centrum in the peripheral parts it may be higher

Tetracycline concentrations decline considerably slower in all tissues studied than those of benzylpenicillin This is surely due to tissue depots of the highly lipid soluble tetracycline (*Schach von Wittenau & Yeary* 1963)

Tetracycline undergoes no essential chemical change in the body (*Kelly & Buyske* 1960 *Eisner & Wulf* 1963) Therefore the level of 10 000 dpm/g found in the tissues corresponds to 1 1 μg/g and can be considered a limit of a therapeutic concentration although the free antibiotic should only be taken into consideration All the vascularized tissues studied except for the retina reach this concentration The low radioactivity in the samples from the retina is partly due to the contamination by the vitreous body The aqueous humor cornea lens vitreous humor and retina generally remain below the therapeutic level Radioactivity in the unvascularized compartments approximates that in the brain at the corresponding time In the vitreous body and retina it is even lower than in the brain The dose of tetracycline injected is relatively lower than that in our experiments with benzylpenicillin when compared with therapeutic dosages generally used Both equal however maximal doses employed in the parenteral treatment of human eye infections

Summary

The distribution of tritiated tetracycline hydrochloride has been investigated in the healthy and bacterially infected rabbit eye In the infected eye higher concentrations were found in the aqueous humor cornea, chorioidea and retina than in the healthy one The greatest concentrations were observed in the ciliary body at most about twice the corresponding blood level The iris chorioidea and sclera revealed concentrations approximating the blood values In these

tissues a therapeutic level of about 1 μg/g is achieved with a dose of 10 mg/kg of body weight Concentrations in the unvascularized compartments the aqueous humor cornea lens and vitreous humor, as well as in the retina remain below this and are at roughly the same level as in the brain

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Larsson Sven Ögat, dets sjukdomar och vård (The Eye Its Diseases and Care) (in Swedish) 2nd ed 176 pp 10 coloured plates and 65 figures Svenska bokforlaget 1969 price Sw kr 29.50

In fact this is the third edition a precursor of the 1960 and 1969 editions having appeared as early as 1935

The many editions are the best proof that the book has fulfilled a mission

The author has had a happy touch in selecting parts of ophthalmology in which a nurse requires special knowledge in order to give satisfaction in a department for eye diseases

Holger Ehlers

Aronson Samuel B et al Clinical Methods in Uveitis The Fourth Sloan Symposium on Uveitis The C B Mosby Company Saint Louis 1968 pp 348 illustrated Price $ 18 25

A number of brief instructive articles and pithy discussions afford an impression of a uveitis symposium held in October 1967 in Baltimore U S A

This symposium was attended by well known specialists int al Zimmerman Kimura Maumenee Gass O Connor Kaufman Perkins from England and Witmer from Switzerland supplemented by an internist an allergologist a statistician and an epidemiologist

Toxoplasmosis and toxocariasis histoplasmosis and other fungal diseases are discussed The common occurrence of spirochaete in the anterior chamber is mentioned Perhaps spirochaete may survive in this very site in spite of an otherwise adequate penicillin therapy

The importance of studying the aqueous humour (Serology cytology) is discussed Anti tuberculous and other uveitis therapy is mentioned Laser therapy as a *prophylactic* measure in toxoplasmosis to avoid recurrence in the direction of the macula, fluorescein angiography and immune electrophoresis are other interesting subjects

It is concluded that the search for the aetiology is hardly of importance in the individual case of uveitis

Future research should be carried out on large collected series It is necessary to distinguish the largest possible number of *varieties of uveitis* in order thereafter to compare the varieties with the results of aetiological tests e g toxoplasmosis neutralization test and focal exudative retinitis Morphologically different disease pictures must be distinguished Stereoretinal *photos should* be sent to various research teams to decide whether it is possible to agree on a common classification prior to a major common research project

The book has an excellent index It may be recommended to all who want orientation concerning the most recent views and projects concerning uveitis

M S Norn

Mikroskopisch histologische Untersuchungsmethoden unter besonderer Berucksichtigung des Sehorgans Published by Professor Dr med habil Andreas Heydenreich VEB Georg Thieme Leipzig 1968 419 pp 11 plates 147 illustrations 41 in colour M 117 –

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Saraux Henri Françoise Rousselie & Gabriel Coscas Optique médicale pratique Édition Doin Paris 1968 416 pp 363 illustrations 12 in colours

The intention of this new book to cover those aspects of optics which are of interest to the ophthalmologist must be said to have been attained in all essentials

The presentation is in 4 parts Part 1 of 156 pages deals with geometrical optics comprising apart from the traditional discussion of reflection and refraction also sections on optical instruments and the optics of the eye

Part 2 is on refraction of the eye examination and anomalies and prescription of spectacles

Part 3 comprises a number of special items such as anisometropia aniseikonia aphakia aids for subnormal vision and contact lenses

Part 4 treats of spectacles frames and glasses uni and multifocal adding a small section on illumination

The presentation is lucid and concise and may be recommended for self tuition

Niels Ehlers

Books on histological technique with a particular view to ocular tissue are rare

This is a comprehensive volume on the subject the technique of preparation the routine histological staining methods as well as histochemical methods being described in great detail Moreover it has a section on the preparation of specimens for electron microscopy

In addition to this general section there is a special section in which the individual ocular tissues are discussed with a view to suitable fixation and staining methods for visualizing the characteristic features of each tissue

This section in particular seems valuable to the ophthalmic pathologist while the general section is perhaps better covered by the current manuals of histological and histochemical technique Nevertheless the book should be on the shelves of any ophthalmic pathology laboratory and incidentally it is of interest to anyone engaged in the morphology of the eye

O A Jensen

Ovesen I Indendors belysningsanlæg 57 pages with illustrations price Danish kroner 15 50 (text in Danish)

Number five of the serial publications on lighting technology has now been issued by the Danish Illuminating Engeneering Society The theme of this part is interior lighting installations and the reader – even an ophthalmologist – is taught in an instructive and comprehensive manner how to calculate the number and placement of lighting fittings and their light sources to obtain a needed level of illumination A topic of special interest to the industry is the calculation of the optimal rate of cleaning and renewal of the light sources The formulas contain a factor for the useful light flux as a function of use and expected sedimentation of dust and a factor for the cost of reconditioning The ophthalmologist may be more interested in the methods of estimating glare and in the list of security limits of disability glare in various workshops

The victims of bad lighting often first present themselves in the ophthalmologist's office contending that something must be wrong with their eyes A knowledge of the basis principles of good lighting is a useful argument in such discussions

V Dreyer

Hollwich Fritz Einfuhrung in die Augenheilkunde 6 Aufl Georg Thieme Verlag Stuttgart 1968 292 pp 340 ill

This concise textbook of ophthalmology published first in 1947 is now being issued in its 6th revised edition It is amply and beautifully illustrated The text is lucid but has avoided any suggestion of a compendium The subject matter is divided in a perspicuous manner according to ophthalmological traditions

Owing to the frequent revisions this book is entirely up to date There is no reason to advance items of minor criticism as it must always be a matter of judgment what is to be included in so brief a presentation

This book covers approximately what is required of medical students in Denmark A few of its therapeutic suggestions seem unfamiliar but the book is recommended as an excellent introduction to ophthalmology

Niels Ehlers

The XXI International Congress of Ophthalmology

will be held in Mexico City from March 8 to 14 1970

The scientific program of the event is the following

I *Special Session*
Manuel Uribe Troncoso Commemorative Lecture

II *Official Subjects*
1 Pathology of the Occipital Lobe
2 Ophthalmic Embryopathies

III *Symposia and Panel Discussions*
1 Recent advances is ocular Histology and Histopathology through Electronic Microscopy
Coordinator Prof J W Rohen (Germany)
2 Modern Problems in children s Ophthalmology
Coordinator Dr Aly Mortada (Egypt)
3 Diseases of the Macula
Coordinator Dr J Donald Gass (USA)
4 Cryosurgery in Ophthalmology
Coordinator Prof Jose Casanovas (Spain)
5 Modern Trends in the Diagnosis and Treatment of Glaucoma
Coordinator Dr R Etienne (France)
6 Selected Subjects in Ophthalmic Therapeutics
Coordinator Dr Irving Leopold (USA)

IV *Session of the International Association for the Prevention of Blindness*
V *Session of the International Organization Against Trachoma*
VI *Free Papers*
VII *Scientific Films*

The numbers of Free Papers will be limited and preference will be given to those dealing with the aforementioned subjects

Applications for participation in the Scientific Program – Free Papers Scientific Films and Scientific Exhibition – must be sent to the Organizing Committee before March 31 1969

There will be simultaneous translation in every conference room the official languages being French Spanish and English

Outstanding personalities of the Ophthalmology all over the world will participate in the Scientific Program

Registration must be done as *Regular Associate* and *Accompanying* members Registration fees are as follows

Regular Members (Ophthalmologists)	$ 60 00 US Cy
Associate Members (Professionals of activities different than Ophthalmology)	$ 40 00 US Cy
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Only the persons registered in the Congress in any of the mentioned categories will be able to participate in the scientific and social activities of the Congress

Every member Regular Associate and Accompanying is entitled to attend – free of

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Every member Regular Associate and Accompanying is entitled to attend – *free of*

charge – two social events Regular Members will receive in addition the Summary and *Proceedings of the Congress* which will be edited in due time

The Organizing Committee has obtained through *Amosa* (a consortium of travel agencies) such advantages as reduction in hotel rates guaranty of keeping those rates unchanged until the celebration of the Congress and confirmation of adequate transportation to every Congress activity

For further information please contact

Secretaria General del XXI Congreso International de Oftalmologia

Apdo Postal 35 528 – Mexico 10 D F – Mexico

Consilium europaeum strabismi studio deditum

Un Congrès se tiendra a Londres sous les auspices du *Conseil Européen* pour les Etudes sur le Strabisme les 25 et 26 Septembre 1969 Les détails et les feuilles d inscription peuvent etre obtenus de Miss Barbara Lee M B E D B O (T) Moorfields Eye Hospital High Holborn London W C 1 Angleterre

The Third International Congress on Neuro Genetics and Neuro-Ophthalmology

is being organized under the auspices of the World Federation of Neurology and particularly by its Research Committee

It will be held in Brussels from the 25th to the 29th of August 1970

The themes of this Congress will be amino acids pathology and *α* gammaglobulinemias The official languages will be English and French

Any of you who would like to participate in this Congress or who would like to receive further information please address yourselves to Professor *Pierre Danis* 15 Avenue de la Folle Chanson Brussels 5 – Belgium

Prof Danis is secretary of the organizing committee

An international congress on ultrasonic diagnostics

will be held in Vienna between June 2 and 7 1969

Inquiries to be directed to

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Holger Ehlers

ANNIS LXX FELICITER EXACTIS DEDICATUM

DIE XXX MAII MCMLXIX

A few months after his seventy-year birthday on May 30th 1969
Holger Ehlers leaves his chair as professor of ophthalmology
University of Copenhagen For more than two decades
Holger Ehlers has been the master of his field and he can look back
on a period marked by growth and expansion
Holger Ehlers is an outstanding leader, intelligence, fantasy,
fundamentally unorthodox thinking and attitude, common sense
and flair for the obtainable and the optimal, engagement
good spirits, physical and mental strength and indefatigability
are proper characteristics No wonder that *Holger Ehlers* –
usually as the chairman – has taken care of a countless number
of scientific, professional, collegiate and practical tasks both
in the ophthalmological and in many other fields
Holger Ehlers must be admired and praised for a multitudinous
fulfilment of activities The ophthalmological sphere may
rejoice the benefit of his ability and never resting mind
Thus during the last fifteen years the Acta Ophthalmologica with
Holger Ehlers as Editor has experienced a period of happy progress
It is with this in mind that the authors of this volume
have dedicated their papers to
the Editor of the Acta Ophthalmologica



ACTA OPHTHALMOLOGICA VOL 47 1969

HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the Department of Ophthalmology (Head Viggo A Jensen)
and the Second Department of Internal Medicine (Head K Lundbæk)
Kommunehospitalet Aarhus University School of Medicine
Aarhus Denmark

FLUORESCENCE ANGIOGRAPHY OF THE IRIS IN DIABETICS AND NON DIABETICS

BY

LAUST H BAGGESEN

In a preliminary communication *V A Jensen* and *K Lundbæk* (1968) described the fluorescence angiographic picture of the iris and reported that leakage of fluorescein was seen at the pupillary border in long term diabetics These studies were done with a Zeiss fundus camera

The present work reports fluorescence angiographic iris studies in a larger group of both diabetics and non diabetics

Method

The studies were performed using a Zeiss Photo slit lamp modified by *J Bruun-Jensen* With this equipment it is possible to take a series of pictures of the iris or any other part of the anterior segment of the eye, in rapid succession

The reason why the photo slit lamp was used instead of the fundus camera was that it was thereby possible to displace the lighthreflex produced by the incomming light towards the periphery of the cornea so that it did not mask the fluorescence angiographic changes at the pupillary border

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The Zeiss Photo slit lamp (fig 1) was fitted with a 7 5 diopter concave lense and a blue filter Schott BG 12 (0 7 mm), in front of the slit opening and a green filter Schott GG 14 (3 0 mm), in the Robot camera s middle ring The generator from a Zeiss Fluorescence angiographic apparatus adjusted to maximum capacity (720 Watt sec) was used as the energy source for the electron flash Photographs were taken at 1 5 sec intervals The flash bulb was aircooled by a specially built in device which prevented dropping out of flashes The film used was Ilford HP 4 (27 29 DIN) and it was overdeveloped approximately 25 % in Ilford Microphen developer The exposures were studied as positive prints enlarged about 5 times Five ml of a 10 % fluorescein sodium solution was given intravenously in a cubital vein as rapidly as possible

The fluorescein circulation time was determined and the presence of extra vascular fluorescence was noted Thereafter the patients could be separated into the following groups patients without leakage – patients with definite leakage + and patients with questionable leakage (+)

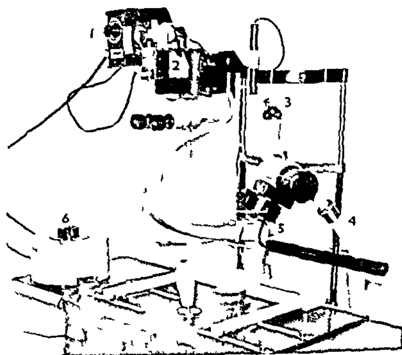


Fig 1
Zeiss Photo slit lamp modified for fluorescence angiography
1) Chronometer and patient data 2) Robot motor camera 3) Blue filter and concave lense 4) Plastic tubing for air cooling 5) Ignition unit for electron flash 6) Transformer for adjustment lighting

Patients

32 non diabetics and 82 diabetics were studied

The non diabetics had no symptoms of diabetes mellitus no glycosuria and a normal fasting blood sugar None of the patients had or had had disease of the anterior segment of the eye These patients were selected from among ambulant patients of the Second Department of Internal Medicine the Department of Neurology and the Department of Ophthalmology The mean age of the non diabetics was 38 1 years the youngest and the oldest being 17 and 67 years

Most of the diabetics were taken from the medical outpatient clinic but some patients from the medical and ophthalmological ward were also used 27 of the diabetics had primary rubeosis iridis diabetica (*Ohrt* 1967) in one or both eyes Mean age of the diabetics was 38 5 years with extremes of 15 and 79 years The mean duration of diabetes was 15 4 years (0 48 years) The ratio between men and women was identical in the two groups and thus the two groups had the same age and sex distribution

Results

A certain amount of time elapses between the injection of fluorescein and the appearance of fluorescence in the arteries of the annulus iridis major There after fluorescence follows the vessels to the pupillary border where vascular bendings could be seen and in some patients a tortuos vessel concentric to the pupillary border Fluorescence then follows the vessels back to the annulus major In some patients it was possible to identify the veins by comparison with photographs taken earlier in the series Fluorescence of the vessels and the bendings becomes gradually weaker but in most cases can still be seen at the termination of angiography (approximately 50 sec after injection)

After fluorescence has appeared at the pupillary border but before it is possible to see the veins filling of the vessels in the collarette can be observed in some patients At about the same time filling of the limbal system of the conjunctiva may be seen

Fluorescein leakage doubtlessly due to an increased capillary permeability for fluorescein can be seen in some patients Leakage appears as luminous dots along the pupillary border which increase in size and gradually coalesce to form a more or less complete ring of fluorescein along the pupillary border In some of the patients exuded fluorescein diffused upwards because of movement in the chamber fluid

Non diabetics

The arm iris time, that is the time from the injection of fluorescein to the appearance of fluorescence in the annulus major, is between 9 0 and 22 5 sec (mean 15 4 sec) Thereafter, fluorescence spreads toward the pupillary border where the vascular bendings can be seen 2 6 sec later (0 6 0 sec) Filling of the veins takes place 5 9 sec (4 5 7 5 sec) after fluorescence appears in the annulus major

Fluorescence angiography of the iris in a non diabetic is shown in fig 2

Leakage of fluorescein was observed in four non diabetics three of which were over 50 years of age and one was 33 years old (fig 3)

Diabetics

In diabetics the mean time from injection of fluorescein to its appearance in the annulus major was 14 9 sec (10 5 22 5 sec) Thereafter fluorescence spread toward the pupillary border which was reached 2 2 sec later (0 7 5 sec) Filling of the veins in the annulus major was seen 5 8 sec (3 0 10 5 sec) after the arteries had been filled Just as in the non diabetics fluorescence persisted in the vessels and bendings throughout the examination

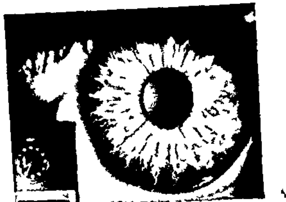
Fig 4 illustrates fluorescence angiography of the iris in a diabetic

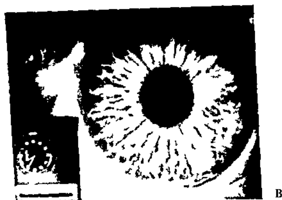
Thus the time it took for fluorescein to pass through the iris was the same in the non diabetics and in the diabetics In order to determine if there was a difference between the individual subgroups the fluorescence angiographic times in the non diabetics without leakage were compared with those in the diabetics with primary rubeosis iridis diabetica and leakage in the same eye If angiographic examination was carried out in both a patient s eyes the results of both examinations were employed Comparison was made using Student s t test with a statistically significant difference at the 95 % level (table 1)

As is shown in table 1 there is no statistically significant difference between arm iris time (A) and artery vein time (C) in diabetics and non diabetics but the time between fluorescence in the annulus major and its appearance at the pupillary border was significantly shorter in the selected subgroup of diabetics (B) In order to elucidate this phenomenon more clearly a comparison was made between the annulus major pupillary border times in non diabetics without leakage and the following groups of diabetics 1) all diabetics with leakage 2) all diabetics without leakage and 3) diabetics without retinopathy and without leakage (table 2)

As can be seen the annulus major pupillary border time was significantly shorter in the diabetics in subgroups 1 and 2 than in non diabetics This was not the case as regards the diabetics in subgroup 3

The occurrence of fluorescein leakage in the diabetics studied appears from fig 5 Just as was the case for the non diabetics the occurrence of extravascular





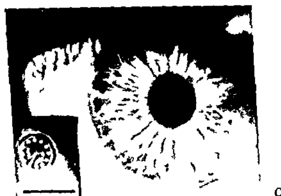


Fig 9

Fluorescence angiography of the iris in a 36 year old non diabetic without leakage of fluorescein A) Fluorescence in the radial vessels of the annulus major (15 0 sec after the injection of fluorescein) B) Fluorescence of the vascular bendings at the pupillary border and of the arteries and veins in the annulus major (74 0 sec after the injection) C) 57.5 sec after injection of fluorescein fluorescence can still be seen in the radial vessels and vascular bendings

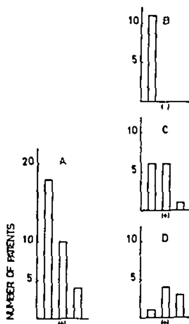


Fig 3

Leakage of fluorescein in non diabetics (– no leakage (+) questionable leakage and + definite leakage) A) All of the non diabetics B) Non diabetics < 30 years of age C) Non diabetics 30 49 years of age D) Non diabetics ≥ 50 years af age

fluorescence increased with age Leakage was however more commen in all age groups among diabetics than in non diabetics In addition fluorescein leakage increased in diabetics with duration of disease Fluorescein leakage was particularly common in patients with rubeosis iridis diabetica where it was seen in 25 of 27 patients (93 %) If on the other hand a comparison is made between the frequency of leakage in diabetics with retinopathy but without rubeosis (6 of 10) with non diabetics it is not possible to demonstrate any difference in frequency of leakage

In patients with primary rubeosis iridis diabetica where fluorescein leakage is particularly marked it was possible in a few cases to see filling of the rubeosis vessels especially in the somewhat larger vessels in the annulus iridis minor and occasionally in the fine vessels of the pupillary border before these became masked by exuding fluorescein (fig 6)

Extravascular fluorescence along the peripheral vessels in the iris was seen in a small number of cases

Fluorescein leakage was greatest in the eye which was most severely damaged by rubeosis iridis diabetica In those patients with unilateral rubeosis definite leakage was seen in some cases only in the involved eye whereas in other cases leakage was seen in the uninvolved eye

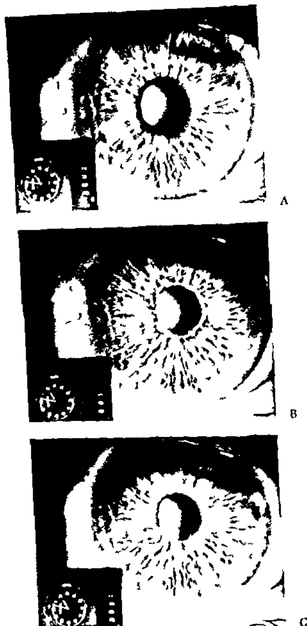


Fig 4

Fluorescence angiography of the iris in a 38 year old diabetic with rubeosis iridis diabetica A) Filling of the radial vessels and vessels of the collarette Luminous dots at the pupillary border (1°0 sec after the injection of fluorescein) B) Leakage of fluorescein at the pupillary border and from the collarette vessels (19 5 sec after injection) C) 48 0 sec after fluorescein inject on The fluorescence has spread across the annulus minor and in the pupil The fluorescence is seen diffusing upwards because of movement in the chamber fluid

Table 1

A comparison of the circulation time of fluorescein in non diabetics without leakage of fluorescein and in diabetics with rubeosis iridis diabetica with fluorescein leakage in the same eye using Student's t test A) arm iris time B) annulus major pupillary border time and C) artery vein time

		A	B	C
Non diabetics	n_1	18	18	14
	$\bar{x}_1$	15.4	3.2	6.2
	s_1	11.67	1.82	1.34
Diabetics	n	25	25	17
	$\bar{x}$	14.5	1.9	5.7
	s	8.76	1.37	1.47
	s_p	9.97	1.56	1.41
	t	0.93	3.34	1.19

$t_{95\%}$ = 1.96 for the number of degrees of freedom over 30

Table 2

Annulus major pupillary border time in non diabetics without leakage of fluorescein compared with 1) all of the diabetics with fluorescein leakage 2) all of the diabetics without fluorescein leakage and 3) the diabetics without retinopathy and without fluorescein leakage using Student's t test

		1	2	3
Non diabetics	n_1	18	18	18
	$\bar{x}_1$	3.2	3.2	3.2
	s_1	1.82	1.82	1.82
Diabetics	n	35	41	15
	$\bar{x}_2$	1.8	2.3	[illegible]
	s_2	1.43	2.14	2.71
	s_p	1.56	2.05	[illegible]
	t	3.89	2.25	1.80

t_{95} = 1.96 for the number of degrees of freedom over 30

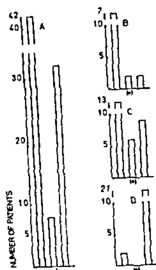


Fig 5

Leakage of fluorescein in diabetics (symbols see fig 3) A) All of the diabetics B) Diabetics < 30 years of age C) Diabetics 30 49 years of age D) Diabetics ≥ 50 years of age

In patients with arterial hypertension proteinuria and elevated serum creatinine fluorescein leakage was seen more commonly than in patients without these changes

A study of the relationship between severity of diabetes as expressed by the treatment necessary for control and the extent of leakage showed that leakage in this study was more common in patients with mild diabetes than in those with severe diabetes Here however age played a role as it was usually the older patients that had the mildest diabetes

Discussion

Fluorescein leakage in the iris on fluorescence angiography has not previously been described in non diabetics In the present study this was found in four of 32 non diabetics Three of these patients were over 50 years of age and one was 33 All four had not only a normal fasting blood sugar but also a normal glucose tolerance test with a two and one half hour blood sugar ≤ 110 mg/100 ml

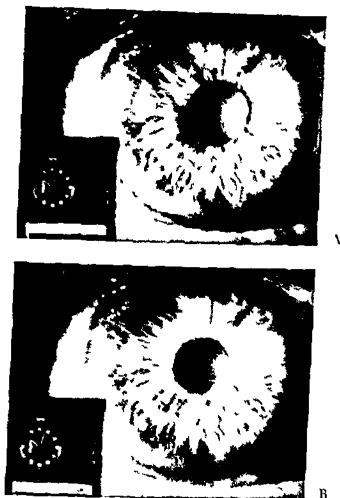


Fig 6

Fluorescence angiography of the iris in a 65 year old diabetic with rubeosis iridis diabetica A) Filling of the rubeosis vessels in the annulus iridis minor superiorly and to the left and at the pupillary border (19.5 sec after the injection of fluorescein) B) Fluorescein leakage in the annulus minor (28.5 sec after injection)

In the diabetics in the present study fluorescein leakage was seen in 31 of the 67 patients with diabetic ocular disease (46%) *Amsler et al* (1947) who studied the blood aqueous humor barrier by measuring fluorescence in the anterior chamber found increased permeability in "40% of diabetics In contrast to the study by *V A Jensen* and *K Lundbæk* (1968) who found more or less pronounced leakage of fluorescein in the iris of all long term diabetics leakage was found in the present study chiefly in patients with primary rubeosis iridis diabetica but not in patients with retinopathy without rubeosis In these patients no difference could be demonstrated on comparison with non diabetics The explanation might lie in the fact that patients with even the slightest ev

dence of neo vascularization were included in the present rubeosis iridis group The finding that fluorescein leakage is primarily seen in patients with rubeosis iridis diabetica is in agreement with what *Heer* (1957) found using Amsler s investigative technique i e that increased permeability was seen in patients with rubeosis iridis diabetica and that many other diabetics studied did not show increased permeability for fluorescein

In the vast majority of cases fluorescein leakage is seen at the pupillary border As mentioned above leakage was seen in a small number of patients in other places in iris In this connection it can be mentioned that diffuse leakage *from the entire anterior* surface of the iris was seen in a patient with secondary rubeosis iridis diabetica who had been studied angiographically for another reason

Summary

Using a modified Zeiss Photo slitlamp fluorescence angiography of the iris was carried out in 32 non diabetics and 82 diabetics 27 of which had primary rubeosis iridis diabetica

In approximately half of the diabetics studied fluorescein leakage was seen at the pupillary border The appearance of this phenomenon increased in frequency with age and with duration of diabetes Leakage was especially common in patients with primary rubeosis iridis diabetica

No difference could be demonstrated between arm iris and *artery vein* fluorescein circulation time in diabetics and non diabetics In contrast the time between the appearance of fluorescence in the annulus major and its appearance at the pupillary border was significantly shorter in the diabetics with rubeosis iridis diabetica and leakage than in non diabetics without *leakage* *No difference* was found between the annulus major pupillary border time in non diabetics and diabetics without retinopathy and without leakage

Fluorescein leakage was seen in four of the 32 non diabetics studied Three of these patients were more than 50 years of age This frequency is not different from the frequency of leakage in patients with diabetic retinopathy without primary rubeosis iridis diabetica

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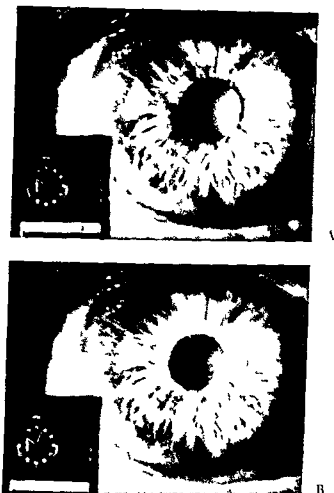


Fig 6

Fluorescence angiography of the iris in a 65 year old diabetic with rubeosis iridis diabetica A) Filling of the rubeosis vessels in the annulus iridis minor superiorly and to the left and at the pupillary border (19.5 sec after the injection of fluorescein) B) Fluorescein leakage in the annulus minor (28.5 sec after injection)

In the diabetics in the present study fluorescein leakage was seen in 31 of the 67 patients with diabetic ocular disease (46%) *Amsler et al* (1947) who studied the blood aqueous humor barrier by measuring fluorescence in the an terior chamber found increased permeability in 40% of diabetics In con trast to the study by *V A Jensen* and *K Lundbæk* (1968) who found more or less pronounced leakage of fluorescein in the iris of all long term diabetics leakage was found in the present study chiefly in patients with primary rubeosis iridis diabetica but not in patients with retinopathy without rubeosis In these patients no difference could be demonstrated on comparison with non diabetics The explanation might lie in the fact that patients with even the slightest evi

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PRESERVATIVES IN EYE DROPS

BY

R BARKMAN M GERMANIS G KARPE and
A S MALMBORG

The importance of eye drops being sterile on use has been increasingly emphasized in recent decades Consequently aseptic preparation sterilization and addition of preservatives are three steps of consequence in their manufacture Another matter of significance is for the drops to be dispensed and dispatched in such containers that infection of the contents is prevented in connexion with their use

Demands for the sterility of eye drops have been introduced into most pharmacopoeias during the past 20 years Pharmacopoea Nordica (1965) prescribes that the eye drops should be prepared aseptically be sterile if they are stored and a suitable preservative added unless the drug has a bactericidal effect. In the pharmacopoeias of other countries as well it is prescribed – or at any rate recommended – that eye drops should contain preservatives Much work has been devoted to finding suitable preservatives (e g *Dale et al* 1949 *Hughson & Styron* 1949 *Theodore & Feinstein* 1952 1953 *Brewer et al* 1953 *Coldstein* 1953 *Klein et al* 1954 *Grote & Woods* 1955 *Lawrence* 1955 *Murphy et al* 19 5 *Riegelman et al* 1955 1956 1958 *Clausen* 1957 *Deeb & Boenigh* 1958 *Whitter* 1959 *Runti* 1960 *Anderson et al* 1964 *Hugo & Foster* 1964)

One of the properties required of a suitable preservative is that it has a rapid lethal effect on bacteria as well as on fungi and viruses (*McPherson & Wood*

Bruun Jensen J Fluorescein angiography of the anterior segment Am J Ophth In press
Heer G Il test alla fluoresceina nella rubeosis iridis diabetica Rass Ital Ottal 26 (1957) 352 363
Jensen V A and Lundbæk K Fluorescence angiography of the iris in recent and long term diabetes Diabetologia *4* (1968) 161 163
Ohrt V Diabetic iridopathy Monography Universitetsforlaget (Aarhus University Press) Aarhus Denmark 1967

The results of previous studies on the antimicrobial effect of preservatives are highly variable It is not always evident whether neutralization of the pre servative s bacteriostatic effect was carried out when the sterility test was made This is nevertheless a factor that may be of great importance when evaluating the results

Development of the eye drop bottle from an ordinary corked bottle with a separate pipette over a pipette bottle to the now commonly used drop bottle with a squeezer which allows instillation without opening the bottle was des cribed by Sandell in Galenisk Farmaci (1967) Even replacement of the bottle with a separate pipette by a pipette bottle decreased the risk of infection of the contents as demonstrated by *Kessler* (1943) Sterility studies of eye drops with out a preservative showed that the incidence of infection – which was 94 % in use of a bottle with separate pipette – fell to 60 % when a pipette bottle was used The Sonyl bottle (see Fig 1) which is well suited for sterile dispensing – in which the dropper is of a chemically resistant plastic material which tole rates autoclaving – certainly implies a further advance No clinical studies de monstrating its ability to eliminate the risk of infection on use have however been made

The irritant effect of the preservative has often been studied in animal expe



Fig 1
Sonyl bottle of resistant glass with a dropper made of a single piece of polyamide Rilsan®

1949 *Engelund* 1956 and others) From a pharmaceutical point of view it should be easily soluble not volatile, and stable, and not be incompatible with the relevant drugs From a clinical point of view, it should not have an irritant effect on the eye Although several chemical substances have been tested none of them has been able to fulfil all these criteria

The substances that have been considered most appropriate and have been most widely used as preservatives in eye drops are the following benzalkonium chloride phenylmercuric nitrate, polymyxin B sulphate phenylethyl alcohol esters of *p*-hydroxybenzoic acid, chlorbutol and neomycin sulphate (*Mun et* 1961 *Foster* 1965)

The preservative s antimicrobial effect has generally been tested *in vitro* but also *in vivo* in animal eyes (*Riegelman et al* 1956 *Kohn et al* 1963) The clinical studies are less extensive

Sterility studies after use by the patients at home were made of eye drops containing esters of *p*-hydroxybenzoic acid (*Kessler* 1943 *Ljungberg & Soderlund* 1945) and phenylmercuric nitrate (Ljungberg & Söderlund) These reports contained a detailed account of the conditions of use The eye drops were supplied both in corked bottles with a separate pipette and in pipette bottles The risk of contamination on use of one or the other type of bottle was tested by concurrent sterility studies of eye drops without preservatives Addition of a preservative decreased the incidence of infection Nevertheless 25 % of the drops provided with esters of *p*-hydroxybenzoic acid and contained in pipette bottles were infected The incidence of infection rose to 55 % when bottles with a separate pipette were used The sterility preserving effect was somewhat better when 0 001 % phenylmercuric nitrate was added

Sterility studies after use at eye clinics have been made with eye drops containing benzalkonium chloride (*McPherson & Wood* 1949), phenylethyl alcohol (*Seedorff* 1960) phenylmercuric nitrate (*Goettsch* 1956) and chlorbutol (*Theodore & Feinstein* 1953 *Altbach & Mazzapica* 1955 *Allen* 1959) All solutions examined proved to be sterile Comparative sterility tests of eye drops without preservatives used under the same conditions were made only by McPherson & Wood After 2 weeks use "an appreciable percentage of them exhibit some degree of bacterial contamination" Detailed information about the mode of storage and instillation was lacking in this report as well as in most of the others mentioned That part of the sterility maintaining effect that is dependent on the type of drop bottle can be judged only in the investigations of Kessler and Ljungberg & Soderlund *Norn & Frolund Thomsen* (1967) studied the sterilizing effect of phenylmercuric nitrate in use of a special drop bottle for mini drops intended for vital staining

Goettsch (1956) gave an account of sterility studies of eye drops collected from ophthalmologists in private practice Similar studies were made by *Vaughan* (1955)

they should be regarded as unsuitable Thus their stability is short and their use can easily give rise to resistant strains

A sterility study was also made of a number of ordinary eye drops without preservatives This was done to ascertain the risk of contamination in eye drops dispensed in bottles with an arrangement for direct instillation

I Study of the Irritant Effect of the Preservatives

Material and Procedure

The irritant effect of the preservatives was tested in 302 persons both healthy volunteers and patients at the Out patient department Most of the latter had either been referred for diagnostic examination of the fundi or had sought advice for an eye disease without irritation in the external parts of the eye

The preservatives tested are shown in Table 1

The preservatives were dissolved in 0 9 % saline to the concentration stated Saline (0 9 %) was used as control The bottles were marked with a code which was not known to the examining physicians All the drops had room temperature (about 20 C)

The investigation was made as a double blind test The bottles were distributed in pairs one for each eye One of each pair of bottles contained saline only The other contained saline with the addition of one of the preservatives At least 50 subjects were tested with each preservative In one group saline only was instilled in both eyes All the subjects were told that the irritant effect of eye drops was being tested and they were given the impression that different drops were being instilled Shortly after instillation they were asked how their eyes felt They were first allowed to give a spontaneous description If they stated that irritation was present more specific questions were sometimes asked about e g smarting itching and a feeling of burning Objective signs of irritation were also registered

Table 1

Preservatives tested for their irritant effect

Benzalkonium chloride	0 02 %
Phenylethyl alcohol	0 50 %
Phenylmercuric nitrate	0 001 %
Chlorbutol	0 50 %
Esters of *p* hydroxybenzoic acid	
Propyl *p* hydroxybenzoate	0 02 %
Methyl *p* hydroxybenzoate	0 04 %

riments (*Hughson & Styron* 1949, *Grote & Woods* 1955 *Heller et al* 1955, *Soerring et al* 1959) These include recording of both objective signs of irritation and pain reactions Different ways of recording and procedure have been used The results are not infrequently contradictory e g with respect to the irritant and tissue damaging effect of benzalkonium chloride

Clinical studies have been reported on esters of p hydroxybenzoic acid (*Kessler* 1943 *Sandell* 1944 *Clausen* 1956), phenylmercuric nitrate (*Ljungberg & Söderlund* 1945) and phenylethyl alcohol (*Seedorff* 1960) Sandell tested 0 9 % saline to which p hydroxybenzoic acid esters had been added in 100 students 83 % reported irritation No irritation was caused by saline alone which was instilled in the fellow eye Clausen ascribed the irritant effect largely to the fall in pH of the solution produced by p-hydroxybenzoic acid esters He found no definite difference between the feeling of irritation after instillation of physiological saline and of 0 08 % Nipasept® solution This was provided that both solutions were of neutral pH and the eye was dried out immediately after instillation On prolonged exposure of the ophthalmic solution on the cornea and the conjunctiva" – which is in fact, the aim in practice – 61 % in a small group studied reported irritation even after neutral Nipasept® solution

Ljungberg & Soderlund instilled 0 9 % saline with the addition of 0 001 % phenylmercuric nitrate in one eye of 120 experimental subjects and saline alone in the fellow eye In no case was any smarting felt on instillation of either solution Seedorff tested phenylethyl alcohol in the same way in 65 subjects All but two reported transient smarting directly after instillation and no reaction in the control eye We have been unable to find any reports of similar, systematic testing of the other preservatives in the literature *McPherson* (1949) and *Altbach* (1955) stated that benzalkonium chloride and chlorbutol respectively produced neither objective nor subjective signs of irritation in clinical use

Present Investigations

A clinical study in which the most common preservatives dissolved in 0 9 % saline were compared to each other with respect to their irritant effect as well as to 0 9 % saline without preservative was carried out at the Eye Clinic Karolinska Sjukhuset in 1963 1964 The preservatives tested and their concentration are listed in Table 1 Polymyxin B sulphate and neomycin sulphate were not included since even from the pharmacological and microbiological aspects

* Nipasept® a mixture of the methyl ethyl and propyl esters of p hydroxybenzoic acid

they should be regarded as unsuitable Thus their stability is short and their use can easily give rise to resistant strains

A sterility study was also made of a number of ordinary eye drops without preservatives This was done to ascertain the risk of contamination in eye drops dispensed in bottles with an arrangement for direct instillation

I Study of the Irritant Effect of the Preservatives

Material and Procedure

The irritant effect of the preservatives was tested in 302 persons both healthy volunteers and patients at the Out patient department Most of the latter had either been referred for diagnostic examination of the fundi or had sought advice for an eye disease without irritation in the external parts of the eye

The preservatives tested are shown in Table 1

The preservatives were dissolved in 0 9 % saline to the concentration stated Saline (0 9 %) was used as control The bottles were marked with a code which was not known to the examining physicians All the drops had room temperature (about 20 C)

The investigation was made as a double blind test The bottles were distributed in pairs one for each eye One of each pair of bottles contained saline only The other contained saline with the addition of one of the preservatives At least 50 subjects were tested with each preservative In one group saline only was instilled in both eyes All the subjects were told that the irritant effect of eye drops was being tested and they were given the impression that different drops were being instilled Shortly after instillation they were asked how their eyes felt They were first allowed to give a spontaneous description If they stated that irritation was present more specific questions were sometimes asked about e g smarting itching and a feeling of burning Objective signs of irritation were also registered

Table I

Preservatives tested for their *irritant effect*

Benzalkonium chloride	0 07 %
Phenylethyl alcohol	0 50 %
Phenylmercuric nitrate	0 001 %
Chlorbutol	0 50 %
Esters of *p* hydroxybenzoic acid	
Propyl *p* hydroxybenzoate	0 07 %
Methyl *p* hydroxybenzoate	0 04 %

riments (*Hughson* & *Styron* 1949 *Grote* & *Woods* 1955, *Heller et al* 1955 *Soering et al* 1959) These include recording of both objective signs of irritation and pain reactions Different ways of recording and procedure have been used The results are not infrequently contradictory *e g* with respect to the irritant and tissue damaging effect of benzalkonium chloride

Clinical studies have been reported on esters of *p* hydroxybenzoic acid (*Kessler* 1943 *Sandell* 1944, *Clausen* 1956) phenylmercuric nitrate (*Ljungberg* & *Soderlund* 1945) and phenylethyl alcohol (*Seedorff* 1960) Sandell tested 0 9 % saline to which *p*-hydroxybenzoic acid esters had been added in 100 students 83 % reported irritation No irritation was caused by saline alone which was instilled in the fellow eye Clausen ascribed the irritant effect largely to the fall in pH of the solution produced by *p*-hydroxybenzoic acid esters He found no definite difference between the feeling of irritation after instillation of physiological saline and of 0 08 % Nipasept® solution * This was provided that both solutions were of neutral pH and the eye was dried out immediately after instillation On "prolonged exposure of the ophthalmic solution on the cornea and the conjunctiva" – which is in fact the aim in practice – 61 % in a small group studied reported irritation even after neutral Nipasept® solution

Ljungberg & Soderlund instilled 0 9 % saline with the addition of 0 001 % phenylmercuric nitrate in one eye of 120 experimental subjects and saline alone in the fellow eye In no case was any smarting felt on instillation of either solution Seedorff tested phenylethyl alcohol in the same way in 65 subjects All but two reported transient smarting directly after instillation and no reaction in the control eye We have been unable to find any reports of similar, systematic testing of the other preservatives in the literature *McPherson* (1949) and *Altbach* (1955) stated that benzalkonium chloride and chlorbutol respectively produced neither objective nor subjective signs of irritation in clinical use

Present Investigations

A clinical study in which the most common preservatives dissolved in 0 9 % saline were compared to each other with respect to their irritant effect as well as to 0 9 % saline without preservative was carried out at the Eye Clinic Karolinska Sjukhuset in 1963 1964 The preservatives tested and their concentration are listed in Table 1 Polymyxin B sulphate and neomycin sulphate were not included since even from the pharmacological and microbiological aspects

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Benzalkonium chlorid	0 02 %
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Phenylmercuric nitrate	0 001 %
Chlorbutol	0 50 %
Esters of *p* hydroxybenzoic acid	
Propyl *p* hydroxybenzoate	0 02 %
Methyl *p* hydroxybenzoate	0 04 %

riments (*Hughson & Styron* 1949, *Grote & Woods* 1955 *Heller et al* 1955 *Sorring et al* 1959) These include recording of both objective signs of irritation and pain reactions Different ways of recording and procedure have been used The results are not infrequently contradictory, *e g* with respect to the irritant and tissue damaging effect of benzalkonium chloride

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also be noted in the groups in which other preservatives were instilled The incidence of a reaction to saline was on the other hand markedly lower in all groups in which a preservative was used than in the control group In this investigation the irritant effect should be evaluated chiefly on the basis of the difference between the incidence of a reaction in the eye in which a preservative was instilled and that in the control eye No subject reacted to saline when phenylethyl alcohol was instilled in the other eye The difference in incidence was also great as far as esters of *p* hydroxybenzoic acid are concerned

The degree of severity of the feeling of irritation produced by the eye drops as well as the objective signs can be seen in Table 3 The subjective reactions to saline alone were vague – I can feel it This also applied to drops with chlorbutol benzalkonium chloride and phenylmercuric nitrate Esters of *p* hydroxybenzoic acid and phenylethyl alcohol on the other hand induced distinct irritation This was generally described by the subjects as smarting Objective

Tabl 3

Inc dence and intensity of subjective and *objective signs of irritation after instillation* of solutions containing different preservatives

Solution	No of subjects	Subjective symptoms No	Subjective symptoms Intensity	Objective signs No	Objective signs Intensity
NaCl 0 9	50	18	*Felt*	–	–
B nzalkonium chloride 0 02%	51	14	Felt	1	Slight conjunct hyperaemia
Phenylethyl alcoh l 0 5	50	39	Smarting	6	Slight conjunct hyperaemia
Ph nylmercuric nitrate 0 001%	50	1°	Felt	1	Slight conjunct hyperaemia
Ch l rbutol 0 5 %	51	14	Felt	–	–
Est of *p* hydroxybenzoic acid	50	36	Smarting	°	Slight conjunct hyperaemia
Pr pyl *p* hy r xyben ate 0 0					
Methyl *p* hydr xybenzoate 0 04					
T t l	30_	133		10	

The relevant soluti n was instilled in one eye an l 0 9% NaCl in the fellow eye
F r explan t on see text p 4( ) and 4(

Results

Table 2 shows that 162 of 302 subjects claimed irritation in one eye soon after instillation. Altogether 115 reacted to drops with a preservative, and 47 to saline alone. Of the latter 18 belonged to the control group in which saline was instilled in both eyes. As previously mentioned, all the subjects had been informed about the object of the test and had the impression that different drops were instilled in the two eyes. The reaction may have depended on two factors, one being the feeling of irritation in the eye that may be produced by instillation of a fluid at 20° C. The other was a psychological factor – *i.e.* information about the aim of the test – which led the subject to try to feel a difference between the right and left eye.

In the groups in which phenylethyl alcohol and *p*-hydroxybenzoic acid esters respectively was instilled in one eye, the incidence of a reaction was noticeably higher (see Table 2). A tendency to an increased incidence could

Table 2

Incidence of subjective irritation after instillation of solutions containing different preservatives and physiological saline

Solution*	No. of subjects	Subjective symptoms of irritations			
		Preservative		0.9% NaCl	
		No.	%	No.	%
NaCl 0.9%	50	–	–	18**	36*
Benzalkonium chloride 0.02%	51	14	28	10	0
Phenylethyl alcohol 0.5%	50	39	78	–	–
Phenylmercuric nitrate 0.001%	50	12	24	7	14
Chlorbutol 0.5%	51	14	28	7	14
Esters of *p*-hydroxybenzoic acid Propyl *p*-hydroxybenzonate 0.02% Methyl *p*-hydroxybenzoate 0.04%	50	36	72	5	10
Total	302	115		47	

* The relevant solution was instilled in one eye and 0.9% NaCl in the fellow eye.
** For explanation, see text p. 465 and 466.

Table 4

Eye drops tested for their sterility after use by the patients at home

Eye drops	No of bottles tested
Atropine 1%	[illegible]
Mintacol 1%	14
Neostigmine 0.3%	1
Pilocarpine 2%	[illegible]1
Pilocarpine 4%	16
Pilocarpine 4% +	
Physostigmine 0.?%	11
Total	[illegible]1

Table 5

Eye drops tested for their sterility after use in wards and Out patient department in 1963 1964 and 1967

Eye drops	No of bottles tested 1963 1964	1967
Atropine 1%	20	9
Atropine 0.5%	9	[illegible]
Fluorescein 1%	4	7
Homatropine 1%	10	8
Methyl cellulose 0 85/100	1	2
Mintacol 1%	5	4
Novesin 0	31	3
Pilocarpine 4%	11	8
Pilocarpine ?%	1	8
Pilocarpine ?% +		
Physostigmine 0.?%	–	4
Pilocarpine 4 +		
Physostigmine 0.5%	14	11
Physostigmine 0.5%	1	
Scopolamine 0.5%	10	6
Tetracaine 1%	31	14
Zinc	[illegible]	3
Total	159	96

signs of irritation in the form of slight conjunctival hyperaemia were observed in only 10 cases in 6 of them after instillation of drops containing phenylethyl alcohol

The investigation thus shows that phenylethyl alcohol and esters of p hydroxybenzoic acid have definite irritant effect both subjective and objective. Nor can it be ruled out that the other preservatives also have an irritant effect

II Sterility Study of Eye Drops Without Preservatives

Material and Procedure

This part of the investigation was intended to ascertain how often eye drops to which a preservative has not been added become infected on use in hospital and by the patient in his home

The sterility tests were made in accordance with the regulations of the National Board of Health for sterility testing of liquid drugs The contents of each bottle of eye drops were tested for their sterility in four substrate tubes. One ml from the bottle of eye drops was incubated for 10 days at 37° C in 15 ml of peptone broth and in 15 ml of thioglycolate broth Incubation was also performed for the same period at 20° C in 15 ml of peptone broth and 7 ml of Sabouraud dextrose broth The inoculate in the Sabouraud dextrose broth was 0 5 ml In addition the same quantity from an unused bottle of each type of eye drops was inoculated in peptone broth with 1 drop of *Staphylococcus albus* culture diluted 1 1000 in thioglycolate broth with 1 drop of *Clostridium butyricum* culture diluted 1 100 and in Sabouraud dextrose broth with 1 drop of *Rhodutorula rubra* culture diluted 1 1000 The antimicrobial effect of the preparation was tested in this way Eye drops with little or no antimicrobial effect were chosen for the tests The drops tested are listed in Tables 4 and 5

The drops were prepared in the customary way according to the prescriptions of the Pharmacopoea Nordica sterile filtered and filled aseptically in sterile 10 ml Sonyl bottles The sterility of all the batches manufactured was checked

For use in the home 71 bottles of eye drops were given to patients at the Out patient department with glaucoma or uveitis (see Table 4) They were returned when the patient came for his next check up which occurred after a period ranging from 5 to 155 days The time for which the drops were used can be inferred from Fig 2 The remaining contents of the bottles were tested for their sterility

The sterility of the eye drops supplied to the three wards and the Out patient department (Table 5) was checked when they had been in use for 1 2 weeks The tests were made during two periods 105 bottles were tested in 1963 and an additional 54 in 1964 A complementary study was made in 1967 All bottles in use in the three wards and the Out patient department were then collected

Table 6
Unsterile eye drops in investigation of sterility in 1967

Eye drops	Microorganism	Comment
Methyl cellulose	Gram neg rods	30 month old solution protective cap missing
Mintacol 1%	Gram neg rods	14 month old solution
Novesin® 0.4%	Gram neg rods	7 month old solution
Novesin® 0.4%	Fungi	7 month old solution
Pilocarpine 4%	Gram neg rods	2 month old solution
Tetracaine 1%	Gram neg rods	1½ month old solution 20 ml protective cap soiled
Total 6 bottles		

as well as phenylethyl alcohol have a pronounced such effect Thus 72% of the subjects given eye drops with the former and 70% of those given the latter reported a transient smarting sensation and in some of them slight conjunctival hyperaemia was observed chiefly in the phenylethyl alcohol group On the whole our results are in agreement with those earlier described with respect to the irritant effect of these preservatives

In our study only the immediate effect after a single instillation was recorded This gives no idea of the irritant effect after lengthy use The irritant effect of a preservative is however a real clinical problem in patients who need eye drops several times a day for years on end Clinical testing during a long period using eye drops containing a preservative as the only potentially irritant substance is nevertheless difficult to carry out A still more difficult matter is to try to ascertain clinically the allergenic effect of a preservative This was not in fact done in our study At the Eye Clinic Karolinska Sjukhuset we have observed a number of patients with glaucoma who had chronic irritation and allergic complaints in the conjunctiva and eyelids which ceased when the preservative was excluded from the eye drops It could therefore be concluded that the complaints were induced by the preservative Formerly it was not obligatory to state the preservative on the bottle s label However since 1965 the Pharmacopoea Nordica requires the nature and quantity of the preservative to be given on the package

The feeling of irritation after each instillation that was demonstrated is however sufficient to question the justification of a preservative in eye drops

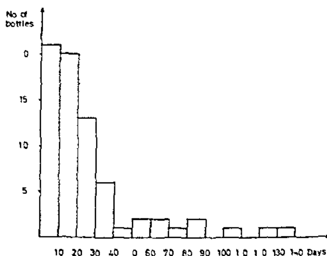


Fig 2
Duration of utilization of eye drops given for use at home.

at the same time On collection the date of dispatch was noted as well as the state of each bottle such as the appearance of the solution soiling of the protective cap or its absence All solutions were dispensed in 10 ml bottles except tetracaine which was dispensed in 20 ml bottles The 96 bottles listed in Table 5 were taken for the sterility study Eye drops with a pronounced antimicrobial effect were excluded

Results

Sterility tests of eye drops given to patients for use at home showed that only 1 of the 71 bottles returned was unsterile It contained 2% pilocarpine and had been in use for 22 days The contents of the other bottles were sterile even up to 133 days use several times a day

After 1-2 weeks use in the wards and Out patient department only 1 of the 159 bottles of eye drops tested for sterility in 1963 1964 was infected This bottle contained 0 5% scopolamine and was contaminated by coliform bacteria

In 1967 when all opened bottles listed in Table 5 were tested for sterility 6 of the 96 were unsterile These had not followed the customary routine at the clinic with replacement every 2 weeks but – after being opened – had stood for a much longer time i e for 1½ to 30 months The results are summarized in Table 6

Discussion

The present study of the irritant effect on the eye of preservatives intended to be added to ophthalmic solutions showed that esters of *p* hydroxybenzoic acid

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The feeling of irritation after each instillation that was demonstrated is however sufficient to question the justification of a preservative in eye drops

Many patients with glaucoma find it hard to use the drops as often as prescribed precisely because of the smarting induced by them. A decrease in the feeling of irritation would certainly help them to follow the prescription.

Our sterility tests showed that eye drops without a preservative, dispensed in a Sonyl bottle, are sterile unless they have been in use for too long a time. Some reservation must nevertheless be made with respect to sterility testing of tetracaine and zinc eye drops. Tests of the antimicrobial effect of the drops disclosed that *Staph albus* could not grow in the presence of tetracaine or zinc. Consequently when the tetracaine and zinc drops were tested for sterility it is possible that an existing contamination by vegetative bacteria could not invariably be demonstrated. A tetracaine bottle was nevertheless among the ... found to be contaminated in 1967. The solution contained gram negative rods. The fact that they could be demonstrated is probably to be ascribed to dilution of the tetracaine with the substrate.

Addition of a preservative and dispensing in bottles that are able to protect against contamination are two ways of maintaining the sterility of eye drops. A preservative cannot replace the demand for sterilization. It is intended to arrest or kill microorganisms that have infected the eye drops after they have started to be used. A preservative is needed as long as a container is lacking which protects against such contamination. The more or less irritant effect is nevertheless a drawback from the clinical point of view. The Sonyl bottle has proved to able almost completely to eliminate the risk of infection during the time of use. In its present design it is however difficult to manage for elderly persons. It would be easier to use if the dropper were to be made longer and softer or if the glass bottle were to be replaced by a squeezable bottle of resistant plastic material. Such squeezable bottles are used by a number of drug manufacturers. The patients generally find them more convenient. If they are suitably designed they should give the same protection against infection as the Sonyl bottle.

The Sonyl bottle was described by *Linde* (1957) who also gave an account of the properties of the plastic material. It tolerates autoclaving and shows good resistance to most chemicals. No mention was however made of the plasticizer used.

Our tests of the sterility of eye drops supplied to the wards and Out patient department showed that it was well maintained on 1-2 weeks use. Contamination could however occur if the bottle had been opened for too long a time. At the Eye Clinic Karolinska Sjukhuset it has for several years been the rule to replace the drops every 2 weeks. This rule should certainly be adopted in places where drops are used for several patients. The length of time for which the drops were used by patients at home before they were tested for sterility can be inferred from Fig 2. Most of the bottles (76 %) had been in use for maximally one month. Sandell suggested in Galenisk Farmaci (1967) that

limitation of the time for use of eye drops in multi dose containers should be introduced One way of achieving this would be to dispense them in smaller containers

Eye drops that are used at operation require special consideration Rigorous demands must be made on their sterility It has long been regarded as un suitable to use a preservative in such eye drops (*Riegelman* 19.8) The internal tissues of the eye are sensitive Moreover the presence of a preservative in eye drops is no guarantee of their sterility Cases of panophthalmitis after operation have been described in which the source of infection was unsterile eye drops *containing* a preservative (*Post* 19.3) The sterility of eye drops to be used in ophthalmic surgery should be ensured by sterilization immediately before opera tion Furthermore they should be used for one patient only One can also use single dose packages if the sterility of the container and the drops is ensured

Summary and Recommendations

1 The irritant effect of the most widely used preservatives for eye drops *i e* benzalkonium chloride chlorbutol esters of *p* hydroxybenzoic acid phenylmer curic nitrate and phenylethyl alcohol was tested in 302 subjects The preser vatives were dissolved in 0 9 % saline and their irritant effect was compared to that of 0 9 % saline alone Esters of *p* hydroxybenzoic acid and phenylethyl alcohol had a definite irritant effect both subjective and objective A tendency to be more irritant than saline alone was noted in the other preservatives tested as well

To ascertain the risk of contamination of eye drops without preservatives dispensed in bottles for direct instillation (Sonyl bottles) a sterility study was made of such drops after their use in hospital and by the patients at home

Of 1 bottles of eye drops given for use at home only one was unsterile The duration of use ranged from 15 to 133 days but 76 % of the drops had been utilized for at most 1 month

Of 159 bottles of eye drops submitted to sterility tests after 1 2 weeks use in wards and Out patient department only one was unsterile

Sterility tests of 96 bottles representing all eye drops in use in the wards and Out patient department on the day of the tests showed 6 to be unsterile All the unsterile bottles had not followed the customary routine at the clinic with replacement every 2 weeks but – after being opened – had stood for a much longer time

3 The following recommendations can be made The demand for a preser vative to be added to eye drops should be abandoned From the clinical point

of view the irritant effect of the preservative is a drawback It can be done without if the drops are manufactured under sterile conditions and dispensed in bottles for direct instillation or if single dose containers are used The length of time for which eye drops are used if they are instilled in several patients, should be limited to 2 weeks, and small containers should be prescribed

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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MORPHOLOGICAL AND HISTOCHEMICAL STUDIES ON FIBRILLOPATHIA EPITHELIOCAPSULARIS

BY

TORSTEIN I BERTELSEN and NIELS EHLERS

In a previous light and electron microscopic study (*Bertelsen Drablos & Flood* 1964) it was shown that in lenses with socalled senile exfoliation (pseudoexfoliation) changes in the lens epithelium and anterior lens capsule were seen apparently specific for this disease On light microscopy a new formed layer (the amorphous layer) was found in the lens capsule lying between the epithelial cells and the original lens capsule (the fibrillar layer) (Figs 1 and 2) at the most peripheral part of the anterior surface of the lens This deep layer had distinct cross striations perpendicular to the surface of the capsule Numerous small dots were found in the fibrillar layer and on the capsular surface a more or less wide spread coating often in the form of bushlike excrescences as described by *Busacca* (1928) (Fig 3) Electron microscopy revealed that these striations in the deep layer consisted of bundles of coarse fibrils which radiated from pits in the surface of the epithelial cells Similar coarse fibrils were found in the dots in the fibrillar layer and also proved to be the main constituent of the substance on the surface Here however they were mixed with thinner fibrils identical with those which form the normal lens capsule On the basis of these findings the authors maintained that the substance visible on the anterior lens capsule in so called senile exfoliation is a fibrillar material formed by the epithelial cells of the lens and proposed the name fibrillopathia epitheliocapsularis (fibrillopathy) for this condition

The addition of ordinary capsule fibrils to the substance on the lens surface was explained by suggesting that these were detached from the capsule during passage of the coarse fibrils Large numbers of the same coarse fibrils were found also between the cells of the iris pigment epithelium The possibility that other structures than the lens might form this pathological substance could not therefore be excluded

Histochemical examination gave no complete answer as to the chemical nature of the coarse fibrils However a glycoprotein seemed to be the most likely

Ashton et al (1965) also observed the changes in the lens capsule but did not describe the changes in the epithelial cells

The present paper comprise the results of some investigations which give new information on the extent of the amorphous layer and its relationship to other structures in the lens together with histochemical data on this layer the dots in the fibrillar layer and the substance on the front surface of the lens

Material and Methods

Seven lenses with fibrillopathy (exfoliation pseudoexfoliation) from patients who also had cataract was examined The lenses were removed intracapsularly without using chymotrypsin and immediately fixed in acetic acid ethanol 25 75 (5 lenses) or 4 % neutral buffered formaldehyde (2 lenses) After 24 hours in the fixative the lenses were transferred to 70 % ethanol where they were kept until dehydration and embedding in paraffin Sections were cut on a Zeiss serial microtome (1180 sections in all)

The routine staining methods used were Masson s trichrome haematoxylin eosin and haematoxylin erythrosin safran The histochemical reactions used are seen in table I Unless otherwise stated reference is made to standard textbooks (*Pearse* 1968 *Lillie* 1965) Six lenses with senile cataract but no clinical evidence of fibrillopathy were used as controls

More than 300 sections were used in digestion experiments with the enzymes pepsin trypsin chymotrypsin papain collagenase amylase hyaluronidase and ribonuclease in the following solutions pepsin (Sigma) 2 mg/ml in 0 02N *HCl* pH 1 6 trypsin (Novo) og chymotrypsin (Novo) 0 1 mg/ml in 0 05 M phosphate buffer pH 8 9 papain (Sigma) 1 mg/ml in 0 9 % saline collagenase (Sigma) 1 mg/ml in 0 9 % saline amylase (Merck) 1 mg/ml in 0 9 % saline testicular hyaluronidase (Fluka) 1 mg/ml in 0 9 % saline and ribonuclease (Fluka) 1 mg/ml in 0 9 % saline The sections were incubated for 15 min to 24 hours at 37° Nearby sections from the same lens were incubated for the same time and the same temperature in the solvent to serve as controls

Results

I *Morphology* The characteristic changes viz the new formed amorphous layer in the lens capsule the dots in the fibrillar layer and the substance on the surface were seen in all the lenses from patients with fibrillopathy but not in any of the controls The amorphous layer was always found in the deepest part

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of the lens capsule In the majority of sections the peripheral limit of this layer was found 5 15 epithelial cells inside the limit of the epithelial layer and in contact with the underlying epithelial cells In some sections however it was found just outside this limit but was then always in contact with the new formed nucleated lens fibres outside the nuclear arc However the outer limit of the deep layer in the next and following sections was often within the outer limit of the epithelium Larger areas were never observed the deep layer al ways being divided up into small islands covering from 5 up to 13 epithelial cells i e an extent of about 50 130 μ

By means of serial sections it was found that islands which were large in one section were small or had disappeared in the next or vice versa The thickness of the amorphous layer decreased evenly from the center of the islands to the periphery (Fig 2) The deep layer appeared as single islands or in groups of two or more islands close to each other sometimes even confluating (Fig 4) In the individual section up to 8 islands were found in the two equatorial zones The distribution in the equatorial zones was never symmetrical and the total width of the area in which the deep layer was found was in no case greater than 1 5 mm The amount of deep layer varied considerably from lens to lens and in the same lens from section to section No increased mitotic ac tivity was seen in the epithelial cells bounding the deep layer

The dots in the fibrillar layer were always most abundant right over the amorphous layer but were also seen just centrally to this The deep layer and the dots in the fibrillar layer were never found in the more central parts of the anterior capsule and in the posterior lens capsule

The substance on the surface of the capsule was found not only over the deep layer but also central to this Sometimes a continuous spongy coating was seen soldering parts of the iris pigment layer to the front surface of the lens (Fig 5 A) Where this fixation was ruptured the substance remaining on the lens surface appeared like the wellknown bush like excrescences of Busacca (Fig 5 B)

The deep layer was visible with all methods staining the capsule and epithe lium With most methods the layer was visible because of a difference in stain ing intensity between the two layers of the capsule A few methods however gave the amorphous layer a different colour from the fibrillar layer In these methods the cross striations in the deep layer the dots in the fibrillar layer and the substance on the surface of the capsule had the same colour whilst the ordinary lens capsule (the fibrillar layer) had another colour This applied particularly to Masson s trichrome staining which stained the first named struc tures red and the capsule blue or green (Fig 1)

II *Histochemistry* The results of the histochemical reactions are seen in Table I Acid mucopolysaccarides could not be demonstrated either in the lens capsule

Table I

Histochemical reactions in fibrillopathy lenses

Reaction	for	Cortex	Ant epith	Fibr layer	*Amorph* layer	Dots in fibr l	Substance *on* lens surf
Toluidin *blue*	Metachromasia	−	±	−	−	−	−
Alcian blue	Acid MPS	−	−	−	−	−	−
PAS (controlled)	Muco glyco lipoprot	−	±	+	±	±	±
Sudan black B	*Lipids*	−	−	−	−	−	−
Metasol fast blue	Lipids	−	−	−		−	−
Mercury orange	Cystein & cystin	++	+	+	−	−	±
Ninhydr Schiff	*a* amino acids	++	+	+	±	±	±
Millon	*Tyrosine*	++	+	−	+	+	+
DMAB (Adams)	Tryptophane	++	+	−	+	+	+
Sakaguchi (Baker)	Arginin	+	−	−	−	−	−
Acid fuchsin (van Gieson)	Collagen	−	−	++	+	+	+
Elastin (Weigert)	*Elastic fibres*	−	−	−	−	−	−
Reticulin Maresch	Reticulin fibres	−	−	−	−	−	+
Bielschowsky	Argyrophilia	−	−	−	−	−	−
Mallory PTAH	Fibrin	−	−	−	−	−	−
Congo red	Amyloid	−	−	−	−	−	−
Methyl green pyronin	Nucleic acids	−	+		−	−	−
Gallocyanin	Nucleic acids	−	+	−	−	−	−

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or in the substance on its surface With toluidine blue the capsule and the substance on its surface were stained orthochromatic light blue The staining intensity diminished when the pH of the staining solution was lowered There was no staining with Alcian blue Attempts to unmask mucopolysaccharides by ninhydrin oxidation of possible competing proteins (*Andersen & Ehlers* 1961) or by digestion with proteolytic enzymes (see below), gave negative results

PAS staining gave a red colour to the fibrillar layer, the deep layer the dots in the fibrillar layer and the substance on the lens surface The reaction was completely blocked by acetylation On subsequent alkaline hydrolysis the reaction in the fibrillar layer was reactivated but not, or only to a minor degree in the pathological substance Also digestion with proteolytic enzymes blocked the PAS reaction completely (Fig 8)

Staining with Sudan black B or Methasol Fast blue showed no evidence of lipids

Mercury Orange gave an intense staining of the lens cortex The epithelium and capsule stained weakly whilst the deep layer did not react The excrescences on the surface of the capsule only gave a very weak reaction The staining was accentuated by thioglycollate reduction but qualitative changes were not seen Ninhydrin - Schiff reactions for α amino acids gave a strong reaction in the cortex and the capsule weaker in the deep layer and the excrescences The Millon reaction for tyrosine strongly stained the cortex The fibrillar layer was not stained whilst the deep layer and the excrescences on the surface were The DMAB reaction for tryptophane gave a very strong reaction in the cortex no reaction in the fibrillar layer and a moderately strong reaction in the deep layer and excrescences Baker s arginine reaction gave a weak reaction in the cortex but did not stain either the capsule the deep layer or the excrescences

The capsule was stained by acid fuchsin (collagen) and the fibrillar layer more intense than the deep layer No reaction for elastic fibres was found Weigert s reticulin staining and silver staining a m Maresch Bielschowsky showed weak and somewhat variable reaction in the excrescences Staining for fibrin (PTAH) and amyloid (Congo red) gave negative results The reactions for nucleic acids (gallocyanin and methyl green pyronin) did not stain the capsule the deep layer, the dots in the fibrillar layer or the excrescences A granular reaction was seen in the epithelial cells which disappeared after digestion with ribonuclease

III *Enzyme digestion* As expected the formalin fixed lenses were not or only very slightly, affected by proteolytic enzymes The results of enzyme digestion experiments on the acetic acid ethanol fixed lenses are seen in Table II After one hour s treatment with pepsin trypsin or chymotrypsin the fibrillar layer in the anterior capsule showed signs of swelling and had lost some of its stainability whilst the epithelial cells and cortex were partly dissolved After 3

Table II

Enzyme digestions – means that the structure is not affected
+ that it is dissolved by the enzyme

	Striations in amorph layer	Rest of amorph layer	Dots in fibr layer	Rest of fibr layer	Substance on the lens surface
Pepsin	–	+	–	+	–
Trypsin/ chymotrypsin	–	+	–	+	–
Collagenase	–	+	–	+	–
Papain	–	+	–	+	–
Amylase	–	–	–	–	–
Hyaluronidase	–	–	–	–	–
Ribonuclease	–	–	–	–	–

hours treatment with one of these enzymes the cortex and epithelial cells were missing except for the nuclei (Figs 6 8)

The resistance of the lens capsule to proteolytic enzymes varied somewhat from lens to lens and in all cases the posterior capsule was considerably more resistant than the anterior The striations in the deep layer the dots in the fibrillar layer and the substance on the anterior surface of the lens were resistant to all three enzymes Owing to dissolution of the surrounding structures probably also that part of the substance on the anterior surface of the lens which according to the electron microscopic studies consists of normal capsular fibrils more than 3 hours treatment with enzymes produced a greater or lesser disorganisation of the substance so that it was readily washed away during the subsequent staining In this respect it was found to be of great importance that the slides were placed horizontally and not vertically during enzyme treatment However even after 18 hours enzyme treatment when the other lens elements except the nuclei of the epithelial cells were completely dissolved or failed to take up dye well preserved excrescences with normal stainability could be found (Fig 9)

In principle papain and collagenase acted in the same way as the proteolytic enzymes mentioned above

On proteolytic digestion of the sections the cross striations in the deep layer and the dots in the fibrillar layer were far more distinct than in sections which had not been exposed to enzyme activity The tissue between the striations in the deep layer reacted as the fibrillar layer and was dissolved whereas the

tissue forming the striations stood out as loose lying threads (Figs 7 & 8) It appeared that the threads in the deep layer were longer than the striations in the nonenzyme treated sections possibly because an intracellular part was unmasked when the cells were dissolved (Fig 8) Where only epithelial cell nuclei remained, the threads were seen to stretch right to these

Hyaluronidase and amylase did not affect the lenses even after 24 hours incubation judged by PAS and van Gieson staining

Ribonuclease did not affect either the amorphous layer or the fibrillar layer nor the substance on the surface of the lens in agreement with the negative reactions for nucleic acids The effect on the epithelial cells is mentioned above

Comments

The extent and form of the amorphous layer does not seem to have been precisely investigated by earlier authors *Bertelsen Drablos & Flood* (1964) found the layer in some lenses as a continuous layer in the intermediate and peripheral parts of the anterior capsule It could however also have a spotty appearance" The posterior limitation was the equator or just behind this as was also found by *Horven* (1966) *Ashton et al* (1965) only found the layer in the anterior equator region The equator region is a very inaccurate statement and since the deep layer according to previous electron microscopic examinations seems to be formed of epithelial cells it must be better to report its extent in relation to these as has been done in the present study

The deep layer consists of a large number of almost circular islands The largest covered 13 epithelial cells i e had an extent of about 130 μ These islands of deep layer lie either alone or in groups in which the islands lie close up to one another or gradually run into one another They are dispersed in a somewhat irregular belt maximum width 1 5 mm the peripheral limit of which corresponds to the epithelial layer s outer limit or rarely just peripheral to this

Horven (1966) believed he had seen deep layer in a few sections which seemed "to be situated in the middle of the capsule In this investigation as with *Bertelsen Drablos & Flood* (1964) *Ashton et al* (1965) and *Larsen* (1968) we always found the amorphous layer in the deepest part of the capsule in contact with the underlying epithelium or new formed lens fibres We believe Horven s findings to be due to an artefact

The earlier electron microscopic study (*Bertelsen Drablos & Flood* 1964) showed characteristic changes in the epithelial cells under the deep layer It was also found that the same coarse fibrils which formed the main component

of the substance on the surface of the capsule were also present in both the deep and fibrillar layer of the capsule These findings strongly suggest that the epithelial cells produce the fibrils The possibility that the process could go in the opposite direction i e that the fibrils invade the capsule from the surface is contraindicated by the observation of normal capsule fibrils in the substance on the surface The electron microscopic findings suggested that these had been torn off from the capsule during the passage of coarse fibrils through it

The present investigation supports the view that the epithelium is the starting point for the pathological substance The deep layer is distributed in islands and is found exclusively in the germinative zone Furthermore it is always in contact with the underlying epithelial cells or new formed lens fibres We can see no explanation as to why a substance which can be found all over the front surface of the lens should only invade the lens capsule at points with such a special localization It is more appropiate to imagine that the spotty appearance is due to groups of cells constituting units which are biologically active in this process

The fact that in some sections the peripheral limit of the deep layer seems to lie outside the epithelial boundary does not contraindicate that the layer is formed of epithelial cells The limit of the epithelial layer is irregular which explains why the boundary of the deep layer may be found outside the epithe lial limit in one section whilst in the neighbouring sections it is often in contact with the underlying epithelium

The attachment of the zonular fibres to the lens capsule is also found in this area However we did not find anything to indicate that the deep layer had any connection with this attachment

That the dots in the fibrillar layer are not only found where the amorphous layer is present but also though to a lesser degree in a small area central to this may perhaps be because the substance from the deep layer penetrates the overlying fibrillary layer to some extent obliquely Another possibility is that it is due to new formation of the lens capsule from the epithelial cells If cap sule formation is greater in the germinative zone than in the central part of the lens it must be assumed that the capsule which is formed at the equator can be gradually displaced in the direction of the center of the lens

Assuming that all substance on the anterior surface of the lens is formed by the epithelial cells in the area where deep layer is found that part of the sub stance which is found central to this must de conveyed there by the aqueous fluid The close contact between the iris and the lens leads to an accumulation of material in the form of the peripheral band whilst only smaller amounts reach the anterior chamber where some of it settles on the lens surface in the form of the central disc Accumulation of substance between the iris and the lens may be so considerable that the two structures become fused together This explains why it is often difficult to get the pupil well dilated in patients with

Fig 1
Deep (amorphous layer with cross striations and fibrillar layer with dots (d) Note the bright red colour of the outer 1/3 of the epithelial cells Masson trichrome with li ht green counterstaining × 500

Fig 2
Deep layer (a) fibrillar layer with dots (d) and a single excrescence on the lens surface (e) The island of deep layer covers only 7 8 epithelial cells Haematoxylin × 500

Fig 3
Fibrillopathy substance on normal anterior capsule (fibrillar layer) Single row of bush like excrescences Note the spongy structure of the substance Haematoxylin Eosin × 500

Fig 4
Arrows points to islands of deep layer in the anterior lens capsule. Haematoxylin × 100

Fig 5 A and B
A Strands of the iris pigment epithelium soldered to the lens capsule through a layer of fibrillopathy substance
B Where the connection is broken the substance on the capsule gets the form of the Busacca excrescences Masson trichrome × 500

Fig 6 A and B
A Effect of 2 hours pepsin digestion B Control section
The fibrillar layer is swollen, and has lost its stainability whereas the deep layer the dots in the fibrillar layer and the substance on the surface are unchanged Masson trichrome × 250

Fig 7
Pepsin digestion 2 hours Fibrillar layer almost dissolved The deep layer consists of loose lying threads The dots in the fibrillar layer and a little substance on the capsule surface are clearly visible Masson trichrome × 500

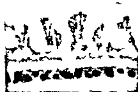
Fig 8 A B and C
Pepsin digestion 3 hours Only remnants of epithelial cell cytoplasma and some cell nuclei are seen Fibrillar layer partly dissolved Deep layer dots in the fibrillar layer and substance on surface clearly visible The threads of the deep layer seems to have elongations into the epithelial cell remnants reaching the cell nuclei PAS haematoxylin × 500

Fig 9
Excrescences from anterior lens surface unchanged after 18 hours treatment with pepsin Haematoxylin Eosin × 100

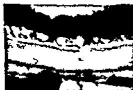

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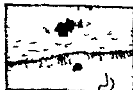

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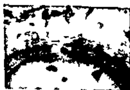

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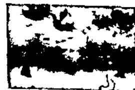

5 B

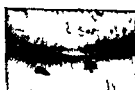

6 A


6 B


7


8 A


8 B


8 C


9

Fig 1
Deep (amorphous layer with cross striations and fibrillar layer with dots (d) Note the bright red colour of the outer ¹/₃ of the epithelial cells Masson trichrome with light green counterstaining × 500

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fibrillopathy and that parts of the pigment epithelium are often removed with the lens on cataract extraction The spongy structure and the special bushlike form of the material which is accumulated behind the iris is in our view due to constant streaming of aqueous fluid through the substance.

Several histochemical studies have been made on fibrillopathia epitheliocapsularis but the chemical nature of the substance has not been clarified *Dvorak Theobald* (1954) and *Arnesen Sunde & Schult Haudt* (1963) thought it was an acid mucopolysaccharide Later investigators (*Bertelsen Drablos & Flood* 1964 *Horven* 1966) however have shown lack of toluidine blue metachromasia and negative Alcian blue reaction which was confirmed in the present study *Thus there is no evidence that the pathological substance is an acid mucopolysaccharide*

The PAS reaction has been the subject of doubt *Dvorak Theobald* (1954) and *Horven* (1966) found a positive reaction in the excrescences whilst *Bertelsen Drablos & Flood* (1964) were of the opinion that the substance on the anterior surface of the lens was mostly negative A positive PAS reaction was found in the present study but however weaker than in the fibrillar layer The reaction was completely blocked by acetylation and was only reactivated to a small degree by subsequent alkaline hydrolysis whereas the fibrillar layer again became strongly PAS positive This suggests that the pathological substance does not contain greater amounts of carbohydrate (*Pearse* 1968) The weak reaction may be due to proteins or in the case of the substance on the anterior surface of the lens mixing with fibrils from the fibrillar layer in agreement with the electron microscopy findings The PAS reaction was negative after digestion with proteolytic enzymes which may be because carbohydrates are split from the normal capsule fibres both in the fibrillar layer an in the substance on the front of the lens

Thus we cannot support Horven s view that the newformed pathological substance is a muco or glycoprotein in that the rather weak PAS reaction can be explained by the presence of normal capsule fibrils which is known to contain about 10 % carbohydrates (*Pirie* 1951)

Earlier investigations have shown tyrosine (*Dvorak Theobald* 1954 *Bertelsen Drablos & Flood* 1964) and tryptophane (*Bertelsen Drablos & Flood* 1964 *Horven* 1966) in the substance on the anterior surface of the lens In this investigation the same amino acids were also found in the deep layer and in the dots in the fibrillar layer On the other hand we have not been able to demonstrate arginine and cystein cystine either in the deep layer the dots in the fibrillar layer or in the substance on the front of the lens and the content of α aminoacids does not seem to be particularly high

It would seem most obvious that the unknown substance should have a protein character The earlier electron microcopic studies in which it was shown that the substance consisted of fibrils with cross striations together with the

Summary

In 7 lenses with fibrillopathia epitheliocapsularis the deep (amorphous) layer was found between the epithelial cells and the true capsule of the lens whilst this was not found in any of 6 control lenses

The deep layer is found in a zone maximum width 1 5 mm along the peripheral border of the epithelium and consists of small islands with diameter up to 130 μ The deep layer has cross striations which on previous electron microscopic examinations has been shown to consist of bundles of coarse fibrils which radiate out from the surface of the epithelium Histochemically these striations the dots in the overlying lens capsule and the substance on the anterior surface of the lens show identical staining properties The same structures are all resistant to the action of proteolytic enzymes in contrast to the rest of the lens Amylase and hyaluronidase did not affect any part of the lens but ribonuclease removed basophilic and pyroninophilic granules in the epithelial cells The histochemical analysis did not result in a final classification of the pathological substance in fibrillopathy A large content of the amino acids tyrosine and tryptophane was found a lesser content of α amino acids and reactions for arginine and cystein cystine were negative Lipids and acid mucopolysaccharides could not be demonstrated just as these was no evidence for the presence of carbohydrates in greater quantities

The investigation supports the view that the pathological substance in the anterior segment of the eye in fibrillopathia epitheliocapsularis is *formed* by epithelial cells in the germinative zone of the lens

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Ashton N M Shakib & R Collyer Electron microscopic study of pseudoexfoliation of the lens capsule I Lens capsule and zonular fibres Invest Ophth (1965) *4* 141 153

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B rt lsen T I Fibrillopathia epithelio capsularis The so called senile exfoliation or pseudoexfoliation of the anterior lens capsule Acta ophthal Kbh (1966) *44* 737 749

Bu acca A Struktur und Bedeutung der Hautchenniederschlage in der vorderen und hinteren Augenkammer Graefes Arch Ophthal (1928) *119* 135 176

content of tyrosine and tryptophane point strongly in this direktion It is however surprising that the substance has been so resistant to proteolytic enzymes *Arnesen Sunde & Schultz-Haudt* (1963) showed previously that the substance was resistant to collagenase whilst the fibrillar layer loses its staining capacity The substance was not affected by trypsin for 2 hours or by pepsin in low consentration (1 mg/ml) for 45 min but it was dissolved when enzyme concentration or incubation time was increased

Our investigations have shown that the striations in the deep layer, the dots in the fibrillar layer and the substance on the anterior surface of the lens is highly resistant both to collagenase pepsin trypsin/chymotrypsin and papain The two firstnamed structures were even more clearly visible after treatment with proteolytic enzymes The striations in the deep layer stood out as loose lying threads as the interjacent tissue was dissolved The study can further indicate that these threads have an intracellular part which can be seen only when the cells are dissolved If this is correct the view that the pathological substance is formed (produced) by the epithelial cells is supported

The histochemical reactions do not give a final answer to the question of the chemical character of the substance found in the anterior segment of the eye in fibrillopathia epitheliocapsularis but they have given some new information In all the investigations carried out the striations in the amorphous layer the dots in the fibrillar layer and the substance on the anterior surface of the lens reacted identical and differently from the true capsule (the fibrillar layer) This applied to staining with Masson s trichrome the histochemical staining reactions as well as the enzyme digestion experiments As the earlier electron microscopic investigations this shows that the striations in the deep layer the dots in the fibrillar layer and the substance on the front of the lens consist of one and the same chemical substance different from the fibrillar layer of the capsule Both the normal capsule fibrils and the coarser fibrils in the unknown substance show cross striations with a periodicity of 510 560 Å (*Bertelsen Drablos & Flood* 1964)

The properties stated do not allow the substance to be identified with a known protein Resistance to proteolytic enzymes is shown by keratin elastin and amyloid Keratin and elastin has no cross striations on electron microscopy Staining for elastin was negative just as elastin has a small content of tryptophane (*Pearse* 1968) Keratin or a parakeratin could agree with the ectodermal origin of the lens but this is not supported by the low content of cystein cystine and arginine Amyloid shows cross striations on electron microscopy and like the unknown substance has a high content of tryptophane and tyrosine and a low content of cystein cystine (*Pearse* 1968) However amyloid contains carbohydrates which could not be demonstrated in these investigations and staining with Congo red was negative Collagen and reticulin which have a fibrillary structure and shows cross striation are readily dissolved by proteolytic enzymes

ACTA OPHTHALMOLOGICA VOL. 47 1969

HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

Charlottenlund Ophthalmic Clinic Denmark

RECONSTRUCTIVE SURGERY IN THE ANTERIOR CHAMBER

BY

JORN BOBERG ANS

Reconstructive surgery in the anterior chamber deals with the reestablishment as far as possible of the anatomical order inside the anterior chamber and is a limited subject related mainly to the treatment of disorders usually caused by external violence inflicted by accidental or surgical trauma

The tissues of the anterior chamber are very delicate even though they stand up to a considerable amount of handling yet they usually remain where and as they are left and never return spontaneously to their original state or place

In every surgical procedure in the anterior chamber it is therefore essential to reestablish the anatomical order and to leave the anterior chamber as close to normal as possible otherwise its complex function may be seriously impaired

The order of the anterior chamber may be disturbed through diseases or through traumae blunt or perforating caused either by accidents or by surgery

Accidental traumae

The need for reconstructive surgery in an eye traumatized through an accident may to a large extent be avoided by means of better primary care This should not be undertaken in a casualty ward but should be given primarily by an experienced eye surgeon

An eye with a perforated injury should be handled and treated as delicately as any other planned intraocular intervention The wound should be cleaned and explored and any possible foreign bodies removed Intraocular haemorrhages should be washed out and bleeding vessels must be found and cauterized even if this involves opening the eye with a new incision

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the eyelids apart and a bridle suture under the superior rectus muscle and sutures under one or two of the other recti if necessary

A small conjunctival flap is usually preferred and the eye is opened ab externo in two planes preplaced sutures are important The opening of the eye should be as large as necessary to get access for free and unhampered manipulations The opening is made with a piece of a razor blade in a special holder bent at different angles and the opening is enlarged with scissors

It is often an advantage to operate under 6 10 even 25 times magnification with the aid of the microscope with both coaxial and slit lamp light

Using Barraquer s small DeWecker scissors and capsular forceps Vannas fine scissors (special models with curved blades straight blades or angled at 45 degrees to the handles) small straight and angled hooks with blunt points but with sharp concave curves and spatulae and repositors of different curves and sizes the anterior synechiae are severed and the posterior synechiae explored and likewise severed

If it is supposed that the zonular treads *are still present* even with a secondary membrane to any unwanted extent alphachymotrypsin is injected Lens matters may be extracted by the Cryo method by the use of forceps or with the Fuchs syringe and it may even be necessary to dissect carefully with knives and scissors

If *vitreous* is present in the anterior chamber a sufficient amount should be *extracted* to permit free manipulation inside the anterior chamber Either the extracted vitreous may be reinjected or donor *vitreous* used at the end of the operation to restore tension and volume to the eye

If vitreous touches the corneal endotheleum *thereby* endangering the cornea it may even be advisable to resort to an *intraocular* lens to keep the vitreous away from the cornea a pupillary lens of the Binkhorst or *Epstein design* is preferred fig 1

Solutions of epinephrine and acethyl choline *Miochol* (Smith Miller & Patch) should be used to dilate or contract the pupil according to the immediate requirements

The angle of the anterior chamber should be explored and synechiae broken by blunt dissection Where *intact* iris tissue is present a peripheral small iridotomy or *iridectomy* may be performed if necessary

If vitreous is adherent to the *anterior surface* of the iris especially in the angle it must be washed *swept or brushed* off and brought back behind the pupil

If a glaucomatous *condition is present* preoperatively and is expected to continue or a rise in tension is feared a filtration operation may be included in the procedure preferably a *Foroni* or a Stallard type of operation

When the incision has been closed with many sutures air must be injected but if the volume of the vitreous or the intraocular *fluid is insufficient* – in

If the lens has been injured, the lens matters should be washed out either primarily or as soon as possible at a later date and not left to be absorbed The iris should be repositioned vitreous prolapses cut off and the vitreous replaced The wound should be sutured carefully in order to obtain a watertight closure air should be injected into the anterior chamber to avoid anterior synechiae and all structures should be brought into their proper places even though this involves another opening of the eye away from the primary wound

In my opinion the cornea should never be covered with a conjunctival flap which prevents inspection of the cornea and anterior chamber a disadvantage which is not outweighed by the possible therapeutic effect of the conjunctival flap Antibiotic treatment should of course be given locally and systemically both before and after the operation The same applies to corticosteroid treatment

Surgical traumae

Surgical procedures may also cause considerable trauma to an eye Insufficient iridotomies with increased intraocular tension may cause iris prolapse or iris incarcerations and anterior synechiae may form Lens matters left in the pupil may give rise to posterior synechiae closure of the pupil rise in intraocular tension vitreous prolapse vitreous loss or vitreous adhesions Without meticulous care in hemostasis intraocular haemorrhages may follow All these serious complications are comparable to the sequelae of any severe trauma

Every attempt to relieve the sequelae caused by such complications should be made in order to correct the damage The eye surgeon should feel obliged to do everything in his power to preserve and restore all possible function to a damaged eye even as little as light perception or vision limited to orientation may prove of importance Such cases have little to loose but everything to gain

It is of course of primary importance to consider the safety of the undamaged eye and one should not hesitate to sacrifice a doubtful blind or nearly blind eye if there is the least possibility of involvment of the good eye

For the damaged eye in question the situation is usually desperate and intervention must be planned and based on thorough examination The preoperative situation must be evaluated and the future development and prospect of the damaged eye and its function assessed and evaluated in relation to the danger of the surgical intervention

The patient should be calm and relaxed and therefore sedation is important In order to obtain as soft an eye as possible Diamox and glycerol are given some time before the operation If the patient is over 12 years of age total anaesthesia is usually not necessary Retrobulbar injection of 2% xylocain adrenalin with hyaluronidase subconjunctival injection of xylocain and akinesia should suffice I usually use an Arruga speculum with sleeve nuts to keep

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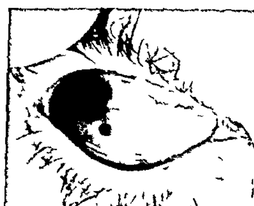
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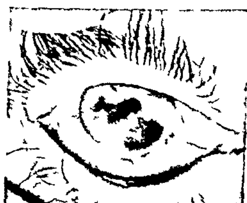
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Fig 1
Pupillary lens of Binkhorst type keeping the vitreous back







Case 4 – Figs 4 5 6
1928 unknown kind of trauma at the age of 2 1967 bullous keratopathy Lamellar graft was suggested elsewhere Vision 2 60 Neither brownish iris spot nor rather invisible corneal scar had been noticed elsewhere The corneal changes were more pronounced in the posterior layers Removal of brownish iris tissue revealed content of iron Corneal changes settled fig 5
1968 successful corneal graft Vision 0 4 incipient cataract explains vision fig 6



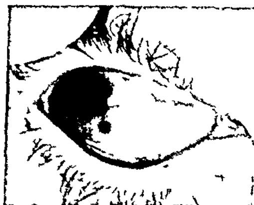


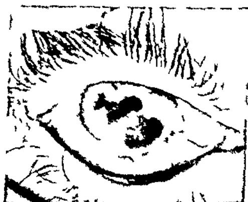
Case I – Figs 2 3

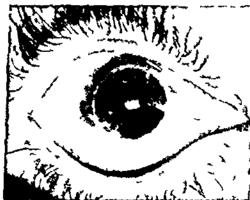
Through an accident 1959 at the age of 6 a piece of a bamboo stick was retained intra ocularly Vision 1/60 1961 reconstruction and removal of the foreign body ultimate vision 0 3 with contact lens



Fig 1
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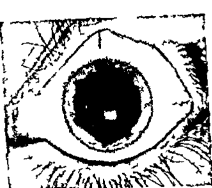
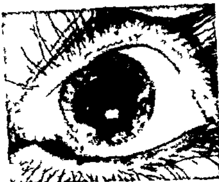
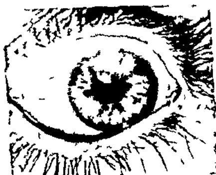
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Case 1 – Figs 2 3

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Case 11 – Figs 7 8 9

Febr 1967 operated a m Fuchs for congen tal cataract of left eye Posterior synechiae deformation of pupil and uneven secondary cataract Vision handmovements March 1967 reconstruction resulting in a clear round pupil improved vision to normal




Case 15 – Figs 10 11

1958 7 mm penetrating graft of left and only eye elsewhere Vision perception of light. Tens on 40 mm Hg January 1961 combined operation for cataract and glaucoma Post perative tension l w and persistent irritation. February 1961 reoperation with patch ing and clos ng of drainage The eye cleared without irritation. Vision 1/60 tension 10 mm Hg May 1961 8 mm penetrating graft. Vision improved to 0 5 The eye without irritation and unchanged at last examination 1968




Case 14 – Figs 12 13

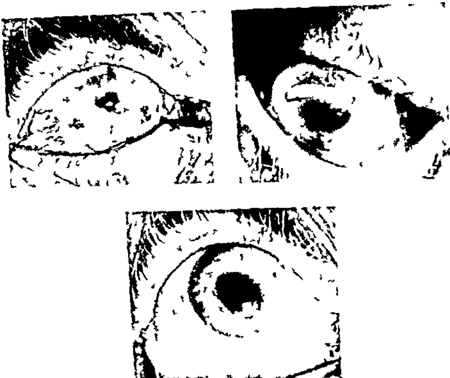
1965 at the age of 62 extracapsular cataract extraction in right and only eye elsewhere Previous iridocyclitis Vision perception of light and localization March 1967 reconstruction with inferior sphincterotomy removal of secondary lens membrane freeing of vitreous adhesions Vision improved to 0 2 September 1967 6½ mm penetrating graft which became clear Vision 0 3 October 1967 fracture of right femur Anticoagulation treatment was instituted November 1967 spontaneous intraocular haemorrhage followed by phthisis

which case the iris will either be pressed too far back or be pushed forward into contact with the cornea closing the angle by air trapped behind the pupil – air must be extracted and sufficient amounts of donor vitreous or balanced salt solution injected into the eye

If the angle will not open it is advisable to use a fine anterior chamber canula curved so as to fit the iris root along the angle With this canula air is injected to free the angle and then to fill the anterior chamber This procedure may be repeated several times before a satisfactory result is achieved If vitreous strands are present these must be severed either with scissors or preferably with blunt manipulation for instance with two very fine long repositors of the Barraquer s design introduced from two more or less opposite positions It may sometimes be difficult to extract the repositor without creating a new incarceration of a vitreous strand but the manipulation will usually be successful by knitting movements with the two spatulae or with one spatula and a syringe fitted with an air canula simultaneously injecting or extracting air

When the surgeon is satisfied in all respects with regard to the repositioning of the structures and the reformation of the anterior chamber the operation may be finished with subconjunctival or retrobulbar injection of antibiotics and steroids the eyelids closed and the eye padded and bandaged Postoperative care does not differ much from the usual treatment associated with other intraocular interventions

For the first three postoperative days the eye should be inspected at least



Cace 15 – Figs 14 15 16

August 1967 spontaneous perforation of Descemetocele in keratitic right cornea at the age of 69 This was treated with an 8mm penetrating graft but no peripheral iridectomies were made Increased tension necessitated fistulizing operation the next day The next morning accidental trauma caused opening of the wound and spontaneous expulsion of the lens Reconstruction with removal of lens matter replacement of vitreous and resuturing Vision 0 2 Graft clear centrally

twice daily but later once daily should suffice Corneal oedema pericorneal injection flare dust or coarser precipitates should be noted The iris should be inspected for edema newly formed or unusually engorged vessels haemorrhage and formation of synechiae which may demand further interventions The vitreous should be inspected the tension checked and the fundus examined for chorioidal or retinal detachments The other eye should be inspected regularly

I usually permit the patient to get out of bed the same day and make him walk up and down the corridor a couple of times

Mydriatics or sometimes miotics metaoxedrine 10 % solution or *epinephrine* and cortisone are instilled into the eye three times a dav *Electrically heated*





Case 14 – Figs 12 13

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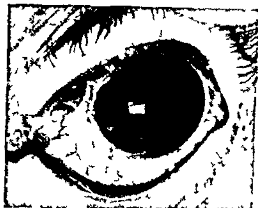
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Original cause of injury	number of cases	results			
		excellent	good	unchanged	worse
Shots	2	2			
Perforating injury	10	8	2		
Disease	2		2		
Perforating injury with retained foreign body	3	3			
Surgical trauma operation cong cat seq	4	3			1 (immediately excellent result but 6 months later detachment unsuccessfully operated)
Surgical trauma operation for cataract	6	5			1 (immediate excellent result but phtisis devel opped after intraocular haemorrhage due to anticoagulant therapy bec use of several fractures)
Total	30	24	4		2

up with sufficient perseverance courage and competence Case number 13 (Figs 10 11) seems to point to the importance of persevering in many cases and especially in those where the ultimate result otherwise will be unavoidable blindness This points to the necessity for reviewing many of the socalled lost cases as well as revising many of the routine procedures especially in the ca sualty ward and introducing a more active attitude towards many cases

Summary

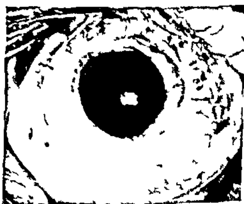
The technique of reconstruction of the anterior chamber of the eye after per forating injuries is described Some cases are cited as illustrations



Case 16 – Fig 17

In a case of lens extraction with a very wide total sector iridectomy and with a bulging soft but solid vitreous prolapse an iris suture proved of great avail in restoring the anterior chamber and improving the intraocular conditions – The Perlon monofilament suture causes no irritation





Figs 18 19

1963 blunt trauma of right eye with resulting irisdialysis and posterior capsular cataract 5 years later irissuture in the 12 1 and 2 o clock position followed by uncomplicated intracapsular lens extraction – uneventful recovery

pads may be given for 20 minutes three times a day and even intramuscular milk injections may prove of value

As appears from the table of the last 30 cases of reconstruction in the anterior chamber 26 eyes were much improved 4 were considerably better and only two were worse

This seems strongly to indicate that the primary care of an injured eye often is insufficient and that unsuccessful surgical procedures not always are followed

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HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

Department of Ophthalmology, Århus Kommunehospital, Denmark
(Head: Viggo A. Jensen)

CATARACT ASPIRATION IRRIGATION WITH TWIN-NEEDLE

BY

JØRGEN BRUUN-JENSEN

In the literature of recent years there has been an increasing interest in aspiration of congenital and soft cataracts. Aspiration of the larger part of the lens substance reduces the post operative reaction, the refracting media become faster more transparent and the repeated discissions of the past can frequently be entirely dispensed with.

Preservation of sufficient depth in the anterior chamber during the entire operation is important for hindering injury of the corneal endothelium, the iris, the posterior lens capsule and the hyaloid membrane. It must however be possible to make the chamber flatter or deeper for the purpose of mobilizing lens substance behind iris. Likewise it must be possible to re-establish the chamber depth if liquid escapes through the corneal incision. Finally there must be an abundant quantity of liquid at disposal for possible removal of the lens substance.

From *Fuchs's* double syringe (1952) a constant volume maximum 2 ml is irrigated and aspirated and thus this instrument cannot be recommended.

Ferguson (1964), *O'Gawa* (1967) and *Girard* (1967) apply a method where irrigation and aspiration take place in separate systems. The irrigation is run by an assistant while the aspiration is made by the operator. With a suture Girard fixes the short irrigation needle at limbus while the aspiration needle is inserted through another corneal incision. Each needle is connected with its own syringe

via a plastic tube Ferguson and O Gawa has constructed special twin needles for insertion through one cornea incision

At the clinic both these methods have been applied for the past two years The writer has constructed a new twin needle by merging two ordinary needles The operational method with this twin needle will be summed up

The twin needle

The component parts of the twin needle (Fig 1) are (1) a 50 *mm long retrobulbar* needle with a diameter of 0 45 mm (the irrigator) and (2) a 30 mm long No 10 needle with an external diameter of 1 00 mm (the aspirator) both of them with a Luer adaptor The points of the needles are rounded but the original oblique cuts are preserved The two needles are merged with a silver plumbing in such a way that the cuts of the needles point away from each other The effect obtained is that the twin needle is more easily inserted through a small corneal incision and that the fluctuation in the chamber during



Fig 1
Twin needle for simultaneous aspiration irrigation

HOLGER EHLERS
ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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CATARACT ASPIRATION-IRRIGATION WITH TWIN NEEDLE

BY

JØRGEN BRUUN-JENSEN

In the literature of recent years there has been an increasing interest in aspiration of congenital and soft cataracts. Aspiration of the larger part of the lens substance reduces the post-operative reaction, the refracting media become faster more transparent, and the repeated discissions of the past can frequently be entirely dispensed with.

Preservation of sufficient depth in the anterior chamber during the entire operation is important for hindering injury of the corneal endothelium, the iris, the posterior lens capsule and the hyaloid membrane. It must, however, be possible to make the chamber flatter or deeper for the purpose of mobilizing lens substance behind iris. Likewise, it must be possible to re-establish the chamber depth if liquid escapes through the corneal incision. Finally, there must be an abundant quantity of liquid at disposal for possible removal of the lens substance.

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Fig 1
Twin needle for simultaneous aspiration irrigation

aspiration irrigation becomes more turbulent Mounted on a syringe the twin needle is easy to handle

Operational method

The operation is made on children in general anesthesia on adults in local anesthesia The pupil suffers maximum dilation with atropine

In a stand next to the operationtable are placed a blood pump and an infusion bottle with isotonic sodium chloride solution A disposable infusion set is connected to the bottle and the tube is led through the blood pump and is connected with the thin needle in the twin needle By revolving the grip of the blood pump an assistant may regulate the speed of the irrigation solution The thick needle of the twin needle is mounted on a 10 ml syringe and with this the operator can make the aspiration by pulling back the piston of the syringe slowly

With a Graefe s knife is made a 4 mm long corneal incision temporally 2 mm inside limbus The point of the Graefe s knife is inserted farther into the anterior lens capsule opening this wide The incision in the cornea is marked with fluorescein the twin needle is inserted and at the same time the assistant fills the chamber Aspiration of the lens substance can now start The operator constantly informs the assistant which depth of chamber is required When the larger part of the lens substance has been removed the eye is illuminated with an ultraviolet cataract lamp herewith the localization of the lens remnants is facilitated The operator tries to remove as much as possible of the lens remnants but without injuring the posterior lens capsule or the hyaloid membrane Lens remnants situated in the periphery must often be left untouched but as a rule the spontaneous resorption of these remnants is quick The operation is finished with a single suture in the corneal incision

Summary

The principles of aspiration irrigation of congenital and soft cataracts are referred A new constructed twin needle and its application during operation is described

Literature

Ferguson III E C A modified instrument for aspiration and irrigation of congenital or soft cataracts Am J Ophth 57 (1964) 596 600

Fuchs J Die Zweigenspritze ein neuartiges Instrument zur Absaugung weicher Stare Klin Monatsbl Augenh *121* (1952) 592 5
Girard L J Aspiration irrigation of congenital and traumatic cataracts Arch Ophthal 77 (1967) 387 91
O Gawa G M Double bore cataract aspiration needle Am J Ophth *64* (1967) 970 2

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reflecting centre in the posterior segment of the fundus in some cases in the macula proper This latter type of extravasations which seems to have been described first by Konigstein in 1881 is considered to be preretinal The appearances are practically analogous with the ocular findings which may be associated with subarachnoid haemorrhages in the adult Histological studies int al by Naumoff Peters and McKeown have confirmed the preretinal site

Incidence Owing to the rapid absorption the incidence of intraocular haemorrhage depends upon the time after birth that the examination is performed From Sanchez Ibanez et al s review of 34 reports it appeared that the incidence was 22 2 % in 24 278 newborns In a Danish series of 594 cases *Wille* (1944) found 42 4 % The incidence immediately after birth may probably be considered to be close on 50 % Frequently the haemorrhages differ in severity in the two eyes but they are bilateral in at least half the cases

Absorption time The round flame shaped and sheet like retinal haemorrhages are absorbed in a few days Their subsidence may be observed day by day and in 5 days the majority have disappeared apparently without leaving traces The absorption of preretinal voluminous haemorrhages of course takes longer according to Vancea two weeks Richman four weeks and Wille observed the persistence of such haemorrhages for 2 or 3 months

These descriptions correspond to my experience During my 10 years as ophthalmological adviser to a paediatric department I have never seen preretinal haemorrhages leave permanent sequelae In one case the absorption of the haemorrhage in the *fovea* was followed by spotty pigmentation indicating macular damage but after these changes had persisted for 2–4 months the appearances returned to normal

Subretinal haemorrhages too may persist for a long time

Only a few cases of vitreous haemorrhage are on record *Schleich* (1890) seems to have been the first to report on a case with blood in the vitreous body The bleeding must have been modest as the vitreous was found to be clear 9 days later In a histological study *Naumoff* (1890) found a hazy vitreous in one case *v Hippel* (1898) mentioned a case of a haemorrhage bursting presumably to the vitreous *v Sicherer* (1907) mentioned a case in which the eye was filled with blood *Edgerton* (1934) found two cases in a clinical series of 458 *McKeown* (1941) *three in 498 Vancea* one in 2_3 while *Richman* (1937) did not observe vitreous haemorrhage among her 531 cases

A study most like mine was reported by *Naunton & Forrester* (1935) who carefully followed a case of bilateral vitreous haemorrhage It is remarkable that in this case the haemorrhage was a late one On the 9th day of life the right eye was normal while on the left the vitreous was hazy and the retinal

veins dilated On the 12th day the entire right vitreous was blurred and on the left the temporal half On the 30th day *the right vitreous was still blurred* while the fundal periphery was visible on the left Thus the vitreous haemorrhage *became aggravated until the 30th* day of life Thereafter, absorption started to that at 7 months there were only a few opacities anteriorly in the right vitreous and one large opacity behind the lens on the left The visual acuity appeared to be normal in this infant who had an alternating convergent squint It was striking that the vitreous haemorrhages remained concentrated unlike the common tendency to dispersion in the adult

The histories of vitreous haemorrhages in 6 newborn infants will be given below

(1) Blegdamshospitalet Paediatric Department 1033/53 A girl born on 4 11 1953 to a primipara Birth weight 1750 g Normal delivery Admitted on the day of birth *because of prematurity Not debilitated Thrived well No oxygen therapy*

26th day of life Right eye Marked haemorrhagic blurring of the vitreous especially in the two temporal quadrants mainly in the form of small flakes but a few large massive clots preretinally Left eye Normal and remained so

33rd day Opacities in the right eye movable and now situated as a haemorrhagic mass in front of the disc

64th day Still opacities in front of the disc and centre but the periphery of the fundus is clearly visible and normal

At 5 months Considerable absorption so that the disc and fundus on the whole *may be seen to be normal* No squint

At 8 months Small residual vitreous opacities

At 12 *months* Normal appearances

Follow up at 14½ years No ocular complaints Visual acuity 6/6 emmetropic in both eyes Ophthalmoscopy clear and normal Of advanced development and intelligent

(2) *Blegdamshospitalet* Paediatric *Department* 1065/53 and the University Hospital Eye Department Blegdamsvej 138/57 A boy born on 18 11 1953 to a primipara Birth weight 2700 g Normal delivery Admitted 4½ hours after birth somewhat debilitated and cyanotic but rapidly picked up Oxygen 33 % for 24 hours Chest radiography and ECG normal Haemoglobin 140–108 % Prothrombin time on the 10th day 91 (normal)

2nd day of life In the right eye slight retinal haemorrhages In the left eye more severe haemorrhagic *extravasation in the retina and preretinal* haemorrhages

9th day Both vitreous bodies hazy with haemorrhages permitting red reflex but obscuring fundal details

19th day Right vitreous clearing but left severely blurred

At 4 months Right vitreous now clear fundus normal Centrally in the left vitreous a dense opacity covering the disc and centre and projecting anteriorly *towards the* posterior surface of the lens Peripheral fundus visible and normal

At 4 years *Admitted* to an eye *department to have an operation* for left sided convergent strabismus Visual acuity in the right eye 6/6 in the left 3/60 The treatment *for the* amblyopia had failed Ophthalmoscopy clear in both eyes

Follow up at 14½ years Visual acuity in the right eye 6/6 -0 75 in the left eye

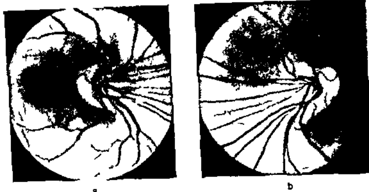


Fig 1 a and b

Case 2 Fundus of right (a) and left (b) eye showing retinal vessels drawn nasally in the peripapillary region

6/36 –? cyl 175° No squint Latent nystagmus occasionally manifest Ophthalmoscopy showed that in both eyes the vessels in the peripapillary regions were of a deviating course as if drawn nasally (Fig 1) Nasally in a juxtapapillary situation there is a thin white membrane presumably on the retinal surface No macular changes except displacement nasally

The boy was well developed

(3) Blegdamshospitalet Paediatric Department 308/59 and the Copenhagen City Hospital Eye Department 555/59 A boy born on 1 4 1959 to a primipara Birth weight 1950 g Normal delivery Admitted 3 hours after birth somewhat debilitated with episodes of rigidity grimacing and brief shrieks Spinal fluid 2/3 mononuclears no red cells protein 170 mg/100 ml Recovered rather quickly No oxygen therapy

Admitted at 4 /2 months to the Eye Department because of lacking visual interest in the surroundings In both vitreous bodies there was a pendulating filamentous opacity containing corpuscles interpreted as red cells Only the extreme periphery of the fundus was visible The condition was diagnosed as neonatal vitreous haemorrhages W R negative Toxoplasmosis reactions negative (neutralization reaction < 1/10 complement fixation reaction < 1/2)

At , months In both eyes Still considerable blurring of the vitreous zonular cataract

At 9 months Absorption discernible

At 13 months Possesses visual orientation. At last the vitreous bodies are so clear that the discs are distinctly visible

Follow up at 6½ years Visual acuity in both eyes 3 60 –1? Nystagmus and zonular cataract Referred to the Institute for the Blind

Had been admitted to a paediatric department for epilepsy at the age of 2 years

(4) Copenhagen City Hospital Eye Department A girl born on 18 8 1965 to a primipara Birth weight 2400 g Normal delivery and thriving At 2½ months she was seen by the author because the right eye remained uncoordinated and the vision in this eye was believed to be impaired

Right eye Opacities looking like fleecy clouds including more intense blurring of the vitreous over the upper half of the fundus which was not visible while the remaining part of the fundus was seen to be normal Left eye normal and remained so The condition was felt to be perinatal vitreous haemorrhage but an inflammatory *lesion could not be ruled out* Paediatric examination Normal X rays of the skull normal Toxoplasmosis reactions normal and W R negative

At 7 months Opacities mainly absorbed

At 10 months Opacities had disappeared *and the fundus was normal*

At 12½ and 17½ months Normal appearances

(5) Blegdamshospitalet Paediatric Department and the Copenhagen City Hospital Eye Department A *boy born on 29 10 1967 to a primipara Birth weight 2650 g* Normal delivery in the right occipito anterior presentation Heart sounds satisfactory throughout but after birth respiratory and cardiac arrest treated with cardiac massage and ventilation for one hour Thereafter spontaneous cardiac action and 20 minutes later spontaneous respiration Transferred to a paediatric department During the first few days of life 2 seizures episodes of cyanosis and of interrupted respiration Oxygen therapy for 72 hours Thereafter he picked up and thrived well

10th and 29th day Right vitreous densely blurred Left eye normal and remained so

At 5 months Convergent strabismus in the right eye A large pendulating opacity centrally in the vitreous body

At 6 months The opacity had diminished a little Peripherally a normal fundus was visible In the slit lamp the opacity was seen to consist of a filamentous meshwork containing brown corpuscles

At 10½ months Now the opacity covers only the disc and the central fundus Otherwise ophthalmoscopy is normal The squint has disappeared and vision seems to be unimpaired when the left eye is covered

At 14 months Vitreous clear fundus normal

(6) University Hospital Eye Department A boy born on 6 3 1953 with craniofacial dysostosis (Crouzon)

17th day Eyes exophthalmic In the right vitreous dense haemorrhagic opacities and in the left a somewhat less marked haemorrhagic blurring

At 6 weeks Right vitreous clearer but still large opacities Left vitreous almost clear with a normal fundus

At 2½ months In the right vitreous a large brownish red opacity behind the lens

At 5½ months Only a few opacities in the right vitreous Fundus normal

Had to be treated for lagophthalmic keratitis

A personal follow up examination was not obtainable but his parents *report that* he is myopic with normal visual acuity The follow up period is considered to be 15½ years

This case was *included although it presents special* features In the presence of the cranial deformity the exophthalmic eyes must have been particularly exposed to trauma in the course of delivery Therefore an individual mechanically conditioned predisposition to neonatal intraocular haemorrhage is believed to have *existed in this* case which will accordingly not be included in several of the following considerations

Discussion

All the deliveries were described as normal All the infants were firstborns and all were premature *the birth weights ranging* from 1750 to 2700 g One

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Data of six cases with vitreous haemorrhage

Patient No	Birth	Birthweight in g	Affected general condition	Oxygen medication	Bilateral	Monolateral	Typical central opacity in v b	Haemorrhage observed after birth	Resorption time m = months	Observation time years	Sequelae
1	normal	1750	—	—		✓		26 d	5	14½	—
2	normal	2700	(+)	1 day	×		×	9 d	4 dxt > 4 sin	14½	nystagmus esotropia amblyopia altered course of retinal vessels
3	normal	1950	(+)	—	×		×	4½ m	13	6½	nystagmus excessive myopia zonular cataract
4	normal	2400	—	—		×		2½ m	10	1½	—
5	normal	2050	+	3 days		×	×	10 d	>10	10/12	esotropia
6					×			17 d	5½	15½	—

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6					×			17 d	5½	15½	—

(Case 5) had been greatly debilitated postnatally having cardiac and respiratory arrest one (Case 3) was somewhat and one (Case 2) slightly debilitated Case 2 has later had epileptiform seizures Two of the infants received oxygen after birth Case 2 for 24 hours and Case 5 for 72 hours In other words the common features are firstborns moderate prematurity and a normal delivery but not a debilitated general condition after birth

The vitreous haemorrhages were bilateral in 3 cases although the severity differed in the two eyes The earliest observation of a hazy vitreous was on the 9th day of life and it is remarkable that in this case (2) the haemorrhage must have occurred late as examination on the 2nd day of life revealed only retinal haemorrhages This applies also to Naunton & Forrester's case An explanation might be haemorrhagic diathesis and the data are not sufficient to reject this possibility entirely The prothrombin time was found to be normal on the 10th day of life menadione was administered immediately after birth and there were no other signs of haemorrhagic diathesis so no systemic factor seems to have been responsible

Since there are now in the literature two examples of late vitreous haemorrhages this might perhaps be a feature in this type of haemorrhage

In three cases (1 5 and 6) the vitreous haemorrhages were observed on the 26th 10th and 17th day of life in routine opthalmoscopy and in two cases (3 and 4) as late as 4½ and 2½ months after birth and then because the parents had the impression that vision was impaired

Three cases (2 3 and 5) showed at a certain stage of the course the previously described characteristic appearance of a large central pendulating opacity in the vitreous body The other cases had smaller and more scattered haemorrhages partly looking like fleecy clouds but mainly collected in lumps The special appearance of the central vitreous opacity must presumably be due to the structure of the vitreous body with Cloquet's canal running through it from the papilla to the posterior surface on the lens Invasion of blood from the area of the disc may be conveyed through this canal which may become as if moulded with a clot Invasion of blood into the vitreous from other fundal regions does not find its way into a similar space and therefore takes on other formations

Haemorrhages in children's eyes as known after trauma usually have a tendency to remain concentrated in the form of drops or strands through a long time corresponding to the firmer structure of the vitreous In adults and especially in the elderly the blood disperses more easily in the looser structure of the vitreous and if the patient is immobilized with the head elevated rapid settling through the liquid phase of the vitreous may occur (*Lincoff 1961*)

The haemorrhagic mass will be transformed into a filamentous meshwork containing red cells and will be gradually absorbed The colour changes from dark red by way of brown into yellow and grey This must represent tra

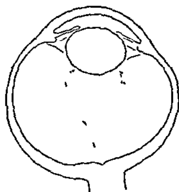


Fig 9
Appearance of pendulating haemorrhagic mass centrally in the vitreous

ditional clotting whose formation and absorption runs a particularly slow course in the special vitreous environment

The mobility of the clot in Cloquet s canal is a characteristic feature The clot appears to be tethered at the disc to reach as far as the posterior surface of the lens It moves with the eye like a barrage balloon in the wind and appears to be of a shape as shown in Fig 2

It is possible that the presence of the clot induces such changes in vitreous structure which increase mobility since otherwise the structure of the new born vitreous would be considered particularly firm However it must be borne in mind that slit lamp examination *in vivo* shows greater mobility with the movements of the eye than would be expected *a priori* In the opinion of the clinician the physical properties of the live vitreous can hardy be checked in the laboratory on enucleated or post mortem vitreous bodies Only it is worth calling attention to the peculiar findings in retinal detachment

The absorption time for vitreous haemorrhage is months in the present cases from 4–13 months This must be due to the very exceptional conditions in the vitreous which differ from any other site of the body where vascularization and cellular activity afford a chance of rapid dissolution of a clot And moreover the clear ocular media give particularly favourable possibilities of observation

In a simplified form the absorption times of intraocular neonatal haemorrhages may be stated as follows Retinal haemorrhages in the course of *days* preretinal haemorrhages in the course of *weeks* and vitreous haemorrhages in the course of months

Among the *causes of extravasations* there is reason to mention first the almost inevitable minor birth traumas which may easily involve congestion

and possibly rupture of vessels These phenomena may probably also occur locally in the eye region without the delivery having otherwise involved any special mechanical difficulties Mayer found haemorrhages to be most likely to occur in large foetuses of primiparae and in prolonged labour but in agreement with Juler, Edgerton and Vancea he could demonstrate no particular relation to mechanical difficulties as reported by McKeown The use of high forceps has been mentioned as a particularly predisposing factor Vacuum extraction as used in recent years is reported to be accompanied by an increased frequency of retinal haemorrhage There is disagreement as to the importance int al of the umbilical cord round the neck v Sicherer s demonstration of particularly pronounced haemorrhages in that half of the face which is mainly exposed during parturition depending on the presentation has not been universally confirmed Some writers e g Millan & San Martin take anoxia and asphyxia to be the most important factor but this view contrasts with the experience of others, e g Juler and McKeown

Analysing 50 consecutive cases that I have had occasion to examine I noticed that no definitive relationship seems to exist between the extent of the intraocular haemorrhage and the severity with which the general condition is affected in particular in the presence of cerebral lesions

In 9 cases I observed what might be called the complete picture of retinal haemorrhage including preretinal extravasation Among these patients 4 had severe cerebral lesions while 2 had only mild lesions and 3 none at all

In 6 infants with moderate retinal extravasation the general condition was moderately to severely affected A small number of retinal haemorrhages was found in 8 infants 5 of whom were moderately affected

Finally normal ophthalmoscopy was recorded in 5 cases of severe and in 22 of moderate postnatal debility

Thus severely affected newborn infants with signs of brain lesion may exhibit both normal conditions of the fundus and very severe intraocular extravasation of blood No correlation has been demonstrated between fundal haemorrhages and ecchymoses in the skin of the face or in the conjunctiva Among the infants who had the cord round the neck some exhibited normal conditions and others pronounced extravasation

Intraocular haemorrhages are presumably in the great majority of cases due to local mechanically determined congestion This hypothesis is supported by the often considerable difference in the extent of haemorrhage between the two eyes

Sequelae of Intraocular Haemorrhage

Since neonatal retinal haemorrhages were recognized it has been repeatedly claimed that they may cause structural derangement which although un

demonstrable in later life may nevertheless cause amblyopia and squinting This has been discussed on paper far more often than assessed clinically by follow up studies In general it seems that considering their high incidence the neonatal haemorrhages must as a rule be harmless

Croci & Scardaccione (1941) claimed there was a relationship between the haemorrhages and subsequent squint and amblyopia but they based their conclusions on a very small series 4 out of 14 cases In a larger series *Bonamour* (1949) found no relationship Among 36 children followed up to the age of 10 years he found 8 to have unilateral amblyopia usually mild Comparison of these results with the neonatal appearance of the fundus gave no basis for deducing a correlation This accords with Štefek s study of 537 children 5 years after birth 104 of whom had presented neonatal haemorrhages Štefek felt that the hypotheses on the named relationship had been proved wrong and concluded that these haemorrhages do not leave visible or functional sequelae and moreover that they were of no significance in assessing the occurence of intracranial haemorrhages

Out of the present 6 cases of neonatal vitreous haemorrhage the permanent sequelae may be definitely assessed in 4 (Cases 1 2 3 and 6) with 14½ 14½ 6½ and 15½ years follow up periods In the monocular Case 1 there were no functional or anatomical sequelae In the binocular Case 2 nystagmus and unilateral amblyopia persist associated with a squint in the eye where the absorption period was longer Possibly these sequelae rest on a purely functional basis being due to anopsia conditioned by the haemorrhages On the other hand the peculiar course of the retinal vessels is no doubt interpretable as an anatomical sequel There seems to be a question of traction involving also the maculas and in a juxtapapillary situation there is a bidimensional epiretinal membrane which presumably consists of connective tissue elements The binocular Case 3 with the excessively long absorption period of 13 months has excessive myopia zonular cataract and nystagmus this boy is under the care for the blind In this case the anatomical and functional condition must be interpreted as a sequel to the massive vitreous haemorrhages

In Case 4 there was apparently no sequel after 18 months follow up In Case 5 the vitreous haemorrhage has disappeared after 14 months follow up and the affected eye has shown convergent strabismus Lastly it has been reported that Case 6 has normal visual function and is myopic

Differential Diagnostic Problems

The rare occurrence of vitreous haemorrhages poses a difficulty and it is an advantage to be familiar with the appearances as described Most certainty

and possibly rupture of vessels These phenomena may probably also occur locally in the eye region without the delivery having otherwise involved any special mechanical difficulties Mayer found haemorrhages to be most likely to occur in large foetuses of primiparae and in prolonged labour but in agreement with Juler Edgerton and Vancea he could demonstrate no particular relation to mechanical difficulties as reported by McKeown The use of high forceps has been mentioned as a particularly predisposing factor Vacuum extraction as used in recent years is reported to be accompanied by an increased frequency of retinal haemorrhage There is disagreement as to the importance int al of the umbilical cord round the neck v Sicherer s demonstration of particularly pronounced haemorrhages in that half of the face which is mainly exposed during parturition depending on the presentation has not been universally confirmed Some writers e g Millan & San Martin take anoxia and asphyxia to be the most important factor but this view contrasts with the experience of others e g Juler and McKeown

Analysing 50 consecutive cases that I have had occasion to examine I noticed that no definitive relationship seems to exist between the extent of the intraocular haemorrhage and the severity with which the general condition is affected in particular in the presence of cerebral lesions

In 9 cases I observed what might be called the complete picture of retinal haemorrhage including preretinal extravasation Among these patients 4 had severe cerebral lesions while 2 had only mild lesions and 3 none at all

In 6 infants with moderate retinal extravasation the general condition was moderately to severely affected A small number of retinal haemorrhages was found in 8 infants 5 of whom were moderately affected

Finally normal ophthalmoscopy was recorded in 5 cases of severe and in 22 of moderate postnatal debility

Thus severely affected newborn infants with signs of brain lesion may exhibit both normal conditions of the fundus and very severe intraocular extravasation of blood No correlation has been demonstrated between fundal haemorrhages and ecchymoses in the skin of the face or in the conjunctiva Among the infants who had the cord round the neck some exhibited normal conditions and others pronounced extravasation

Intraocular haemorrhages are presumably in the great majority of cases due to local mechanically determined congestion This hypothesis is supported by the often considerable difference in the extent of haemorrhage between the two eyes

Sequelae of Intraocular Haemorrhage

Since neonatal retinal haemorrhages were recognized it has been repeatedly claimed that they may cause structural derangement which although un

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Seissiger J Arch f Augenh 101 302 1929
v Sicherer Ber d deutsch ophth Gesellsch Heidelberg *34* 210 1907
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will be felt in the presence of typical pendulating opacity built up of a mesh work containing corpuscles The same applies if the vitreous haemorrhages are observed *during the first days of life to co exist with retinal extravasa* tions But normally, the diagnosis will be deferred until several examinations have been performed as any major opacity of the vitreous body obscuring major segments of the fundus may easily cover fundal lesions Traditionally, tumour and *inflammatory lesions will come to mind These cases make a great impres* sion upon the examiner, and together with the parents some months have to be spent in uncertainty

Summary

While neonatal haemorrhages are common ocurring presumably in one half of all newborns vitreous extravasation is rare in newborn infants These haemorrhages may present themselves in a particular characteristic form the *blood collected as a pendulating opacity centrally in the vitreous body* The absorption takes months The vitreous haemorrhages may entail permanent visual impairment and anatomical sequelae

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which is used to record the corneal pulse This phenomenon was found to be related to the fact that the bulb is pressed into the orbit at loading and it seemed possible that it was due to kinking of small orbital arteries supplying the bulb (*Bynke* 1968 b) However it is not only the position of the bulb but also its shape that changes at loading The cornea is flattened and the length of the bulb is shortened *Barany* (1908) suggested that the reduction of A_{10} was related to this deformation since a given increase of volume would be expected to produce a smaller increase of pressure in a deformed bulb than in a spherical one The underlying idea is this Injection of a small volume of fluid into a primarily deformed bulb will in the first place change its shape towards spheri cal and there will be no distension of its walls On the contrary even a small injection into a primarily spherical bulb cannot change its shape without distending its walls – Another aim of this study was to find out whether the drop of A_0 at loading may be caused by the deformation of the bulb *(II)*

Material and Methods

Nineteen rabbits weighing 2 8–3 8 kilograms were used for the experiments

Anaesthesia was induced and maintained by intravenous mebumal sodium (ACO) about 120–180 milligrams for each rabbit In addition four per cent Xylocain (Astra) was instilled into the eye to be examined

The pulse synchronous oscillations of IOP and the mean IOP were recorded by means of two pressure transducers connected to the cannulated anterior chamber by a teflon tube and the corneal pulse by means of a piezo electrical instrument hanging on the bulb at the examination (for details cf *Bynke* 1968 b)

The pulse amplitudes were measured in millimetres and their changes in per cent of the initial values Each calculation was based on mean values of about 4–8 consecutive waves from repeated experiments The mean IOI was measured in mm Hg but changes of IOP after injection (cf below) in millime tres only

I In 8 rabbits the pulse synchronous oscillations of IOP and the mean IOP of the right eye were recorded immediately before during and immediately after the right common carotid artery had been closed for about 10 seconds In these experiments the artery lumen was momentarily closed and opened again by means of a clamp A similar technique has been used by *Barany* (1946) The carotid manipulations were repeated in each rabbit In some ex periments IOP was allowed to change spontaneously with a change of the artery lumen. In others it was kept at a constant level artificially In one of

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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FURTHER STUDIES ON THE OCULAR PULSE IN RABBITS AT EXPERIMENTAL CAROTID OCCLUSION AND AT LOADING OF THE BULB

BY

H G BYNKE M D

Introduction

This is an additional study of two problems which appeared in the author s previous investigation about the ocular pulse They are partly connected and their solution seems to be of both physiological and clinical interest

Closure of the ipsilateral common carotid artery in rabbits is accompanied by a reduction of the amplitude of the pulse synchronous oscillations of IOP (A_{io}) and of the corneal pulse (A_{corn}) This must be a consequence of a damping of the pulsations in intraocular arteries mainly in the choroid (cf *Bynke* & *Schele* 1967) But the mean IOP also decreases on carotid closure (*Barany* 1946 *Davson* & *Matchett* 1951 *Kornbluth* & *Linner* 1955 *Bynke* 1968 a) Further more A_{io} and A_{corn} rise and fall with the mean IOP even in the absence of any carotid manipulation (*Lawrence* & *Schlegel* 1966 *Bynke* 1968 b) It is therefore natural to suggest that the ocular hypotension after carotid closure may contribute to the reduction of A_{io} and A_{corn} – One of the aims of this investigation was to verify the existence of such a contributive mechanism and to evaluate its size *(1)*

A_{io} also drops as soon as the bulb is loaded by a piezo electrical instrument

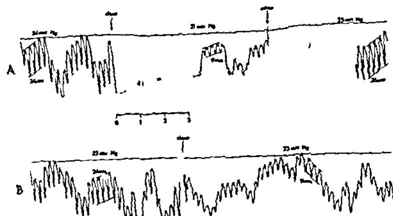


Fig 1

Mean IOP (upper curve) and pulse synchronous oscillations of IOP (lower curve) at momentary closure and opening of the ipsilateral common carotid artery in one rabbit. The frequent pulse waves superpose the slower and larger respiratory variations The mean IOP was allowed to change spontaneously (A) resp kept constant artificially (B)

rabbits the reduction of A, was greater when the mean IOP was allowed to decrease than when it was kept constant

In the sympathectomized rabbit the results were similar to those of other animals *(Table 1)*

Statistical calculations by means of the t test (paired observations) showed that the reduction of IOP was significantly greater when the initial IOP was 35–40 mm Hg than when it was 18–26 mm Hg ($p < 0.01$) The reduction of A_{io} was found to be almost significantly greater when the mean IOP was allowed to decrease than when it was kept constant ($p < 0.05$) whether the *initial* IOP was low or high

In the other 8 rabbits in which the artery lumen was gradually closed at a constant mean IOP the course of the pulse reduction varied individually On an average the reduction started during the initial closure phase and was possibly greater during the first than the second half of the procedure *(Fig 2)* The course of the unloaded reduction curve (A in the figure) seemed to be steeper than that of the loaded curve ($A_{(L)}$) Thus on an average the reduction of A was 57 per cent and that of $A_{(L)}$ was 48 per cent The reduction of A was relatively small i e 28 per cent

In order to test the significance of the difference between the reductions of A and A_L a comparison of the regression coefficients of the two curves was made in the interval between 100 and 20 per cent lumen area in which both

these animals a cervical sympathectomy had been performed six days previously

In 8 other rabbits the pulse synchronous oscillations of IOP the mean IOP and the corneal pulse of the right eye were recorded during gradual closure of the right common carotid artery by means of a clamp adjustable by a micrometer caliper (*Bynke* 1968 a) Throughout these experiments the mean IOP was kept at a constant level of 25 mm Hg The recordings were made with the bulb unloaded resp loaded by a piezo electrical instrument weighing 9 gm

II A small syringe adjustable by a micrometer caliper was attached to the teflon tube connecting the anterior chamber and the pressure transducers By rapidly turning the micrometer screw a constant volume of 1 7 cu mm of isotonic saline solution was injected into the right eye of 8 rabbits in the course of about half a second The injections were made with the bulb 1) unloaded 2) loaded with a piezo electrical instrument weighing 20 gm and 3) loaded with this instrument and simultaneously raised a few millimetres from its orbital bed by traction in sutures previously fixed in the bulbar conjunctiva around the limbus The sutures ran around a pulley fixed above the eye and their free ends were loaded with another weight of 20 gm The initial mean IOP was constantly kept at 25 mm Hg The pulse synchronous oscillations of IOP and the mean IOP were recorded immediately before and after the injections The experiments proved to be fairly well reproducible

Results

I Each momentary occlusion of the carotid artery was accompanied by prompt and simultaneous reductions of the mean IOP and of A_{10} As soon as the artery was opened again both variables reached their initial values In 4 rabbits the final values even surmounted the initial ones by 1–2 mm Hg resp 10–50 per cent (*Fig 1*)

In 8 rabbits in which the initial mean IOP was 18–26 mm Hg the reduction of the mean IOP was 2–9 mm Hg (av 6) and the reduction of A_{10} was 45–86 per cent (av 68) When the mean IOP was kept constant in these animals the reduction of A_{10} was 40–86 per cent (av 61) In 4 of the 8 rabbits the reduction of A_{10} was greater when the mean IOP was allowed to decrease than when it was kept constant (*Table 1*)

In 5 of the mentioned 8 animals the experiments were repeated starting at a mean IOP of 35–42 mm Hg Then the reductions of IOP and of A_{10} were 7–23 mm Hg (av 14) resp 58–91 per cent (av 76) When the mean IOP was kept constant the reduction of A_{10} was 58–88 per cent (av 70) In 4 of the 5

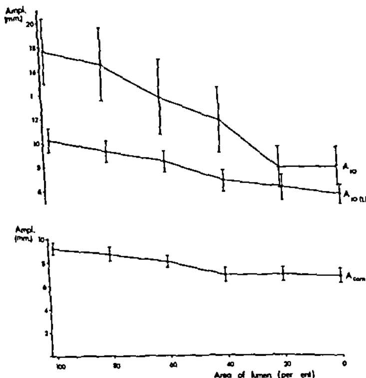


Fig. 2

The amplitude of the pulse synchronous oscillations of IOP with the bulb unloaded (A_0) resp loaded with a piezo electrical instrument weighing 9 gm ($A_{10(L)}$) and of the corneal pulse (A_{corn}) during gradual closure of the ipsilateral common carotid artery in 8 rabbits The mean IOP was kept constant at 25 mm Hg Each deviation represents one standard error of the mean

II The mean IOP increased after each injection of 1 7 cu mm saline solution in the 3 eyes in which these experiments were performed The increase was regularly smaller when the bulb was loaded than when it was unloaded or loaded and simultaneously raised from its orbital bed *(Table 2)* Further more A_1 and the increase of IOP after injection (ΔP) were about proportional in experiments on the same animal Thus the quotient A_{10} ΔP was 0 2 0 2 resp 0 2 in the first rabbit 0 2 0 3 resp 0 4 in the second and 0 6 0 7 resp 0 6 in the third

On the basis of these figures it was also possible to calculate *approximately* the size of the pulse volume which was found to be 0 2 to 0 7 $\times$ 1 7 cu mm i e 0 3 to 1 2 cu mm

Table 1

Initial mean IOP, IOP reduction and reduction of the pulse synchronous oscillations of IOP (A_{10}) in the right eye of 8 rabbits at momentary occlusion of the ipsilateral common carotid artery

Rabbit No	Initial IOP (mm Hg)	IOP reduction (mm Hg)	A_{10} reduction (per cent)
VI G 12	26	9	68
	21	0	58
VI R 9	25	3	64
	25	0	40
V Y 5	20	3	67
	20	0	67
VI G 9	26	2	69
	25	0	64
	40	*7*	*65*
	41	*0*	*59*
V R 17[1]	26	8	70
	24	0	56
	42	*16*	*75*
	42	*0*	*60*
VI R 20	18	9	72
	20	0	75
	38	*23*	*91*
	38	*0*	*88*
VI R 21	19	7	45
	21	0	45
	35	*16*	*58*
	35	*0*	*58*
VI R 22	25	6	86
	25	0	86
	40	*9*	*90*
	40	*0*	*85*
Arithmetic mean	23 1	5 9	67 6
	22 6	0 0	61 4
	39 0	*14 2*	*75 8*
	39 2	*0 0*	*70 0*

[1] sympathectomized

curves were about linear The statistical calculations showed that the slope of A_{10} was significantly steeper than that of $A_{10(L)}$ ($p \approx 0\ 01$)

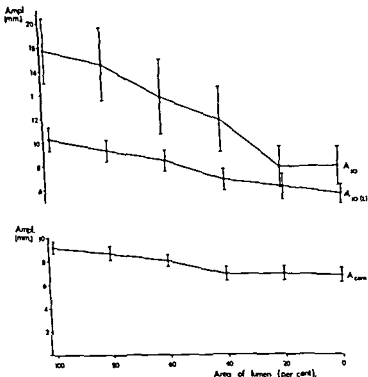


Fig 2

The amplitude of the pulse synchronous oscillations of IOP with the bulb unloaded (A_0) resp loaded with a piezo electrical instrument weighing 9 gm ($A_{10(L)}$) and of the corneal pulse ($A_{c\,r}$) during gradual closure of the ipsilateral common carotid artery in 8 rabbits The mean IOP was kept constant at °5 mm Hg Each deviation represents one standard error of the mean.

II The mean IOP increased after each injection of 1 7 cu mm saline solution in the 3 eyes in which these experiments were performed The increase was regularly smaller when the bulb was loaded than when it was unloaded or loaded and simultaneously raised from its orbital bed *(Table 2)* Furthermore A and the increase of IOP after injection (ΔP) were about proportional in experiments on the same animal Thus the quotient A Δ P was 0 2 0 2 resp 0 ° in the first rabbit 0 2 0 3 resp 0 4 in the second and 0 6 0 7 resp 0 6 in the third

On the basis of these figures it was also possible to calculate *approximately* the size of the pulse volume which was found to be 0 2 to 0 ı × 1 7 cu.mm ı e 0 3 to 1 2 cu mm

Table 1
Initial mean IOP IOP reduction and reduction of the pulse synchronous oscillations of IOP (A_{io}) in the right eye of 8 rabbits at momentary occlusion of the ipsilateral common carotid artery

Rabbit No	Initial IOP (mm Hg)	IOP reduction (mm Hg)	A_{io} reduction (per cent)
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	21	0	58
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	40	*9*	*90*
	40	*0*	*85*
Arithmetic mean	23 1	5 9	67 6
	22 6	0 0	61 4
	39 0	*14 2*	[illegible]
	39 2	*0 0*	*70 0*

[1] sympathectomized

curves were about linear The statistical calculations showed that the slope of A_{io} was significantly steeper than that of $A_{io(L)}$ ($p \approx 0\ 01$)

accompanied by a smaller increase of IOP when the bulb was loaded than when it was unloaded or loaded and simultaneously raised from its orbital bed Furthermore in experiments on the same subject the size of A and that of the increase of IOP were about proportional These results support the hypo thesis that the reduction of A_0 on loading is mainly or exclusively related to deformation of the bulb

The calculated size of the pulse volume was similar to that obtained from other experiments (*Lawrence & Schlegel* 1966 *Bynke* 1968 b)

Summary

The pulse synchronous oscillations of IOP the mean IOP and the corneal pulse in rabbits were recorded by a previously described experimental equipment In 16 animals the lumen of the ipsilateral common carotid artery was mo mentarily or gradually closed In 3 animals rapid intraocular injections of a small volume of saline solution were made with the bulb unloaded resp loaded with a piezo electrical instrument It was found that

1) Carotid closure is accompanied by ocular hypotension which contributes to the damping of the ocular pulse but this effect is small

2) A light piezo electrical instrument is probably theoretically preferable to a heavy one in the diagnosis of carotid occlusion

3) The damping of the pulse synchronous oscillations of IOP at loading is mainly or exclusively due to deformation of the bulb

Acknowledgements

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Table 2

Amplitude of pulse synchronous oscillations of IOP (A_{11}) and increase of mean IOP (ΔP) after rapid injections of 1 7 cu mm isotonic saline solution into 3 rabbit eyes
Values in millimetres

Rabbit No	Bulb unloaded			Bulb loaded			Bulb loaded and raised		
	A_{10}	ΔP	A_{10} ΔP	A_{11}	ΔP	A_{11} ΔP	A_{11}	ΔP	A_{11} ΔP
VII R 10	5	24	0 2	2	12	0 2	5	21	0 [illegible]
VI R 5	5	28	0 2	2	7	0 3	3	8	0 4
VI R 24	5	8	0 6	2	3	0 7	3	5	0 6

Discussion

I The fact that carotid closure produced an instantaneous reduction of the mean IOP probably means that the reduction is mainly due to a decreased filling of the intraocular vascular bed However an additional effect due to a decreased formation of aqueous as found by *Barany (1947)* and *Kornbluth & Linner* (1955) cannot be excluded That the reduction of IOP was greater at a high than at a low initial pressure was to be expected from simple physical reasons

After carotid closure the reduction of A_{10} was found to be greater when the mean IOP was allowed to decrease than when it was kept constant This supports the hypothesis that the co existing ocular hypotension contributes to the reduction of A_{10} We may assume that it also contributes to the reduction of A_{corn} since previous experiments have shown that there is a parallel change of both pulse amplitudes But this effect of the hypotension is obviously small Thus in the present experiments less than 10 per cent of the average reduction of A_{10} could be attributed to the ocular hypotension *(Table 1)*

After opening of the artery lumen the mean IOP and A_{11} in some experiments reached values above the initial ones This rebound phenomenon has been observed previously *(Bynke 1968 a)*

During gradual closure of the carotid artery the reduction of A_{11} was greater when the bulb was unloaded than when it was loaded with the piezo electrical instrument Consequently it seems that a light instrument is theoretically preferable to a heavy one in the diagnosis of carotid occlusion On the other hand a very light instrument has the practical disadvantage of slipping off the cornea during recording

II Rapid injection of a small and constant volume of saline solution was

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HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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Head of the Eye department Professor B Lø...t

OCCUPATIONAL POSSIBILITIES OF COLOUR DEFECTIVES

BY

V DREYER

The purpose of most of the colour vision examinations made at an eye clinic is do decide whether or not an applicant fulfills the visual requirements of the traffic sector Many eye clinics have only pseudo isochromatic plates and often only plates approved for licence issue in this special country This routine can easily have as a shortcoming that the ophthalmologist gets a biased idea of the problems and possibilites of colour blind subjects and it may e g make it difficult for him to give advice if a principal has doubts about the employment of a colour blind apprentice Furthermore pseudo isochromatic plates are used as the only standard at psychotechnical tests of apprentices Such processes are strongly rejected by *Cowan* (1942) who states clearly and briefly that the value of a pseudo isochromatic plate as regards prognoses of occupation is comparable to a visual acuity chart containing nothing but 6/6 letters Pseudo isochromatic plates can be used only to decide whether the colour sense is normal or not and besides this decision is not clear

General methods of examination

Any clinical test for screening anomalous subjects from a large group of normal subjects must have an accuracy which is reached by setting up a separation

Read for the Danish Ophthalmological Society March 30th 1968

Barany E The influence of intraocular pressure on the rate of drainage of aqueous humour Stabilization of intraocular pressure or of aqueous flow? Brit J Ophth *31* (1947) 160 176

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Table I

Diagnoses possible with Nagel s anomaloscope

	trichromates		dichromates
protan	protanomaly	extreme protanomaly	protanopia
deutan	deuteranomaly	extreme deuteranomaly	deuteranopia
colour amblyopia			

colour blind persons with *Nagel's* anomaloscope On the one side one can group colour blindness in the subtypes protans and deutans these types being interrelated with regard to the spectral location of confusion colours and on the other side a classification can be made in trichromates and dichromates as the first mentioned mix red and green to yellow in a ratio turning aside from the normal while the last mentioned match any mixture of these two colours with standard yellow if only the luminance of this is adjusted The extreme anomalous fall outside the system they form a group of their own in a mid position between the trichromates and the dichromates The diagnosis colour amblyopia is used about a group that misreads pseudo isochromatic plates but gives *Nagel* values within the normal range however with wide spread range of acceptances

The introduction of Nagel s anomaloscope formed a culmination a development which had had as its purpose a refinement of colour vision diagnostics It was a remarkable benefit to be able to stop to regard colour blindness as a unity and the grouping in types got great importance in genetic research The practical importance of the clinical sub grouping was the next impelling one The fact that most of the anomalous trichromates do not realize their defect till they are examined while most of the dichromates have reali ed their handicap in their everyday life might indicate that the unsafest condition is that of being a dichromate It does not however suggest that anomaloscopic classification need necessarily have the same vocational validity The Nagel test admittedly makes it possible to judge qualities like colour fatigue matching range and increased sensitivity to colour contrasts and these qualities vary within the single diagnostic group but still safe standards for the importance of the qualities in everyday life are wanted

Navigation railway traffic and aviation

It is commonly agreed that normal colour vision must be demanded in the

between normality and abnormality Seen from a historical point of view the only purpose of colour vision testings was to judge the capability of the subject of observing hues and marking off colour tints Thus the first clinical tests simply consisted of presentations of coloured material *Seebeck (1837)* could with the help of coloured pieces of paper find some persons with deficient colour perception but here in Scandinavia we refer especially to *Frithiof Holmgren* who in 1878 introduced his test with about 15 cm long skeins *Holmgren's* skein test was later approved for colour vision tests used for seamen's licences *The test is* made up of a selection where the subject sorts out hues matching a previously chosen standard skein A carefully made *Holmgren's* test could disclose half of what we call colour deficiency today In that way in Denmark *de Fontenay* (1879) was able to show that among 5300 male persons the frequency of colour blindness was 3 5 % Later on *Krenchel and Daae* changed *Holmgren's* test by cementing 1 cm woollen samples on a plate These minor objects were harder to mark out than were the skeins The test was however inferior *to the skein test because the selection of hues was smaller and that one could* not group the colour samples but only name them

The development in railway traffic and navigation had the effect that more advanced processes of examination had to substitute the primitive colour selection tests The demand for maximum colour discrimination with shipmasters and engine drivers grew more and more impending and requested refined diagnostics which could not be given by the skein test and its modifications a fact *that the frequences quoted themselves suggest Stilling (1877) was the first* to state the principle of pseudo isochromatic plates Since then a long series of plates based on this principle have been developed for clinical uses Among pseudo isochromatic plates *Ishihara's* whose first edition came in 1917 is second to none Since 1912 a violent struggle went on in Sweden to have *Holmgren's* skein test abolished as the approved testing device but not *until 1944* grew the joint plate set *Bostrom II and Boström Kugelberg* the only official Swedish test The proposal to have a pure Swedish plate set approved did not spring from national price but was made in order that the quality of the test battery should always agree with the official demands In Norway and Denmark where *Ishihara's* plates are approved too a dilemma may arise because the authorities have no influence on the colour rendering quality of the separate *editions of the plates*

Nagel's anomaloscope was first designed for clinical use in 1907 and this instrument was generally agreed to be the safest means of getting an precise colour deficiency diagnosis

The test is based upon a matching of a mixture of red light of 670 nm wave length with green light of 546 nm wave length with a standard yellow colour of 589 nm wave length Table I shows the diagnostic types that will be the issue of an examination of

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	trichromates		dichromates
protan	protanomaly	extreme protanomaly	protanopia
deutan	deuteranomaly	extreme deuteranomaly	deuteranopia
colour amblyopia			

colour blind persons with *Nagel's* anomaloscope On the one side one can group colour blindness in the subtypes protans and deutans these types being interrelated with regard to the spectral location of confusion colours and on the other side a classification can be made in trichromates and dichromates as the first mentioned mix red and green to yellow in a ratio turning aside from the normal while the last mentioned match any mixture of these two colours with standard yellow if only the luminance of this is adjusted The extreme anomalous fall outside the system they form a group of their own in a mid position between the trichromates and the dichromates The diagnosis colour amblyopia is used about a group that misreads pseudo isochromatic plates but gives *Nagel* values within the normal range however with wide spread range of acceptances

The introduction of Nagel s anomaloscope formed a culmination a development which had had as its purpose a refinement of colour vision diagnostics It was a remarkable benefit to be able to stop to regard colour blindness as a unity and the grouping in types got great importance in genetic research The practical importance of the clinical sub grouping was the next impelling one The fact that most of the anomalous trichromates do not realize their defect till they are examined while most of the dichromates have realized their handicap in their everyday life might indicate that the unsafest condition is that of being a dichromate It does not however suggest that anomaloscopic classification need necessarily have the same vocational validity The Nagel test admittedly makes it possible to judge qualities like colour fatigue matching range and increased sensitivity to colour contrasts and these qualities vary *within the single* diagnostic group but still safe standards for the importance of the qualities in everyday life are wanted

Navigation, railway traffic and aviation

It is commonly agreed that normal colour vision must be demanded *in the*

between normality and abnormality. Seen from a historical point of view the only purpose of colour vision testings was to judge the capability of the subject of observing hues and marking off colour tints. Thus the first clinical tests simply consisted of presentations of coloured material. *Seebeck* (1837) could with the help of coloured pieces of paper find some persons with deficient colour perception, but here in Scandinavia we refer especially to *Frithiof Holmgren* who in 1878 introduced his test with about 15 cm long skeins. *Holmgren's* skein test was later approved for colour vision tests used for seamen's licences. The test is made up of a selection where the subject sorts out hues matching a previously chosen standard skein. A carefully made *Holmgren's* test could disclose half of what we call colour deficiency today. In that way in Denmark *de Fontenay* (1879) was able to show that among 5300 male persons the frequency of colour blindness was 3.5 %. Later on *Krenchel and Daae* changed *Holmgren's* test by cementing 1 cm woollen samples on a plate. These minor objects were harder to mark out than were the skeins. The test was however inferior to the skein test because the selection of hues was smaller and that one could not group the colour samples but only name them.

The development in railway traffic and navigation had the effect that more advanced processes of examination had to substitute the primitive colour selection tests. The demand for maximum colour discrimination with shipmasters and engine drivers grew more and more impending and requested refined diagnostics which could not be given by the skein test and its modifications, a fact that the frequences quoted themselves suggest. *Stilling* (1877) was the first to state the principle of pseudo-isochromatic plates. Since then a long series of plates based on this principle have been developed for clinical uses. Among pseudo-isochromatic plates *Ishihara's*, whose first edition came in 1917, is second to none. Since 1912 a violent struggle went on in Sweden to have *Holmgren's* skein test abolished as the approved testing device, but not until 1944 grew the joint plate set *Boström II and Boström-Kugelberg* the only official Swedish test. The proposal to have a pure Swedish plate set approved did not spring from national price but was made in order that the quality of the test battery should always agree with the official demands. In Norway and Denmark, where *Ishihara's* plates are approved too, a dilemma may arise because the authorities have no influence on the colour rendering quality of the separate editions of the plates.

Nagel's anomaloscope was first designed for clinical use in 1907 and this instrument was generally agreed to be the safest means of getting an precise colour deficiency diagnosis.

The test is based upon a matching of a mixture of red light of 670 nm wave length with green light of 546 nm wave length with a standard yellow colour of 589 nm wave length. Table I shows the diagnostic types that will be the issue of an examination of

(1) processes requiring maximum colour vision
(2) processes where minor defects are acceptable
(3) processes where defects in colour perception are of no importance

Graded formulations of colour vision requirements are more just to the colour blind but are at the same time more requiring as regards the medical evaluation than the rigoristic either or which held good before at the evaluation of applicants to occupations within the traffic sector

At an evaluation of the practical possibilites of the capabilities of colour blind people it must be realized that colour perception like other visual functions is limited by a series of thresholds No human being is able to identify colured objects subtending subliminal visual angel or coloured objects of sub threshold brightness The level of adaptation and the colour of the background are also critical for the perception of colour The localization in the visual field is likewise of importance as the perception of colour is limited by isopters whose excentricity depends on the colour of the test object from the campimetry we know that the isopter for red and green are found in a more central position than the isopter for yellow and blue In this way a series of threshold values limits normal perception of colour but the colour blind person differs from the normal in that all these threshold values are increased and the more so the more grave the colour blindness is There is a solid request for a *clinical test which* can judge not only qualitative but also quantitative aspects of colour deficiences regarding the threshold conditions existing during the performance of many work processes

Test for occupational fitness

In the instructions for Ishihara s plates it is stressed that the plates can be used for differentiated diagnostic purposes *Completely colour* blind subjects must make °0 errors while partly colour blind subjects make but 16 A *definition* however is wanted of the exact meaning of the words complete and *incom*plete As will be shown later on the proposal that *the amount of* errors is proportional to the seriousness of the defect of colour vision will not suffer closer examination Furthermore the plate set is supposed *to make possible* a differentiation between protans and deutans by means of *the plates* where digits in various tints of red are seen on a grey background *It is stated* that the deutans are incapable of reading the brick red *digit while* the protans are incapable of reading the red purple digit in these plates *Wieland* (1933) and *Hansen* (19(3) however demonstrated that the rule *held good* in only about 60 % respectively 80 % of their *series* Some inverse answers were found and many colour blind could read none of the *digits* whatever Ishihara s statements admittedly hold good at a *statistical* record but have little predictive value when one wishes to use them in the individual case

fields of navigation and railway traffic. The unfortunate choice of red and green as signal colours in these branches *of traffic are incapable of change The* choice is motivated traditionally having as its origin the purely technical dif ficulties of past ages in making especially blue *signal colours of proper bright* ness A shipmaster or an engine driver will encounter situations where he must be able to discern the signal at a so long distance and under so unfavourable conditions of visibility that even a slightly deficient colour vision endangers the traffic safety

The beginning of this century saw a beginning of growth of aviation side by side with a progressive development in the field of radio communication and the possibility seems to have arisen that this sector of traffic could have freed itself from optical signalling In the teeth of this however the development has led to an farreaching ause of coloured light signals in airports and in the cock pits of the planes and once again part of the colours happened to lie among the confusion colours of defectives Most countries, therefore, require normal colour vision from pilots

Other occupations

The interest in industrial ophthalmology is on the increase the branch how ever, is still in its earliest stage A close analysis of industrial work proces ses and a definition of the standard for visual demands from workers within the individual crafts have not yet been performed this also including the colour sense *The military authorities of many countries however have been* pioneers in questions concerning occupational visual standards A defence organization administrates many branches of work and in this way becomes a state inside the state In the armed forces a medical evaluation before service grading is a time honoured proposal and the military ophthalmologic board were here forced to consider the importance of various colour sense defects in practical workshop service and other specialized military services too It must be only too evident that in vocations outside the traffic sector one cannot afford to reject about 8 % of all male applicants The military and later the commer cial aviation were the first to cease to require the highest degree of *colour* vision in the members of the air crew who are not pilots in command In the internationally adopted medical requirements of *health for aviation personnel* it is stated in a few words that holders of licences "shall be required to demon *strate his ability to perceive readily those colours* the perception of which is necessary for the safe performance of his duty Corresponding regulations are found for the naval forces of many countries (deck duty however colour safe personnel) and for army workshop personnel In agreement with this an attempt has been made at an industrial ophthalmologic symposium in New Orleans (1964) conducted by *Noval* to adopt the classical grouping a *large* number of work processes in three categories

prenticeship in a series of crafts hand in hand with the discharge of one s con scription *Ishihara s* plates (10th ed) were used as a screening device and all anomalies of colour vision found were examined with anomaloscope to state the differential diagnosis Some underwent supplementary examinations with *Bostrom Kugelberg* and *Bostrom II* some with the *American AO H R R plate* some with *Farnsworth Panal D 15* and finally some with *Danish Standard (3)* Colours for Labelling

The use of the lastmentioned test has its own overture The standard sheet is a Danish norm for the colours used for labelling of pipelines compressed air containers and other colour labelling in the field of industry Such codes are always sent out for critical evaluation before they are adopted The ophthalmological profession objected because it was seen that many colour blind persons would be unable to discriminate the colours proposed However the code shared the fate of the signal colours Even if it had been possible to choose labelling colours which also colour blind had been able to mark out, the system adopted was incapable of change When the standard was published the *Eye Clinic* Rigshospitalet Tagensvej made pilot enquiries which dis closed that a simple naming of the colour samples of the standard sheet mashed to ? × ?5 cm was applicable to an occupational selection of colour blind subjects In some respects this process represents a return to the processes first used in examinations of colour vision The processes however are no longer used for diagnostics *but for* qualitative evaluations of defects of colour vision.

Table II sums up the number of plates of Ishihara s plate set misread compared to the various types of colour blindness diagnosed with Nagel s anomaloscope A general feature is that increasing number of errors *agree with more* serious defects of colour *vision* *In this way all* dichromates misread over half of the plates On the other hand many misreadings are also often found *in* persons suffering from minor defects *Among the* deuteranomalous more than

Table II

Misreadings Ishihara s plates 10th ed (148 subjects)

	Deuter anomalous	Prot anomalous	Deuter anopia	Prot anopia	Extreme Deuter anomalous	Extreme Prot anomalous
0 errors	1					
1 [illegible] errors	1	[illegible]			1	
8 14 errors	14	3	1		[illegible]	
[illegible] errors	39	16	[illegible]0	15	8	4
[illegible]	6[illegible]	[illegible]1	31	15	11	4

In the United States of America the Second World War disclosed a request for an all Americal test plate set Till then the German and Japanese plates had been used *Hardy Rand and Rittler* (1945) began the work of making a plate which could not only screen colour deficient subjects but which could also serve as an instrument in a qualitative evalutation of the type and extent of the colour sense defect Through a scoring sheet the type diagnoses protan tritan and tetartan are made in the same way the grades mild medium strong can be evaluated In a paper from 1954 the authors compare the new constructed plates with processes used before the standard for the selection of the colour blinds being more than three errors in *Ishihara s* plates or more than two misreadings in *Boström Kugelberg s* test set This standard for the normality is however, less clear than the one used here in Scandinavia where faultless reading is required This suggests that some colour blind persons showing minor defects have been left out in the comparative studies *Hardy Rand and Rittler* found maximum agreement between the earlier processes and their new plates where the response wanted was whether or not the colour vision was normal The classification in protans and deutans was made with *Nagel s anomaloscope* and the plates were trustworthy in 97 % among deutans and 100 % among protans When the AO H H R plates showed unclassifiable type this was always caused by minor defects in colour vision Finally with regard to separation in mild medium and strong defects the AO H R R plates were found to be superior to other tests and were held to be the most fortunate choice in practical assistance in choice of vocation

In 1947 *Farnsworth* launched his Panel D 15 Actually he adopted Holmgren s time honoured idea for a test originally used for grading of personnel in the U S Navy Farnsworth s test set consist of 16 small circular chips coated with Munsell paper colours carefully selected among the colours that colour blind subjects confuse The so called reference chip is placed in the box and the examinee is asked to put the chip with the greatest likeness to the reference chip next to it This process is carried on till all the chips which carry a number on their rear side are put in the box Then lines joining the numbers of chips are plotted The normal pattern becomes a circle joining numbers in numerical order while in the case of colour blindness lines joining the scores produce diagonal lines placed round a protan a deutan or a tritan axis

Author s Investigations

The purpose of the investigation reported below has been the attempt of trying which process fits best to consider the occupational fitness of a colour blind subject The material includes 232 colour blind subjects all of them examined at the Clinic of Aviation Ophthalmology *Most of the examinees* were applicants for the Air Force School for Professionel Enlisted Men Here one can get ap

neither Bostrom Kugelberg nor Bostrom II nor both in combination are suitable for an evaluation of the occupational fitness of the subject examined

Table V shows a summary of the data of 35 colour blind subjects examined with the American AO H R R plates First one must note that 12 % passed the test in spite of the fact that using the approved Scandinavian tests they must be recorded as colour blind The type diagnosis was correct in only 29 % of the deutans and in 69 % of the protans estimates deviating substantially from the authors own suggestions Finally with regard to the evaluation of the seriousness of the colour blindness the table shows that only 46 % of the dichromates were classified as seriously colour blind Thus a prognosis regarding fitness for occupation based on the AO H R R plates does not seem clear

59 colour blind persons were examined with *Farnsworth s Panel D 15* Mis readings occurred as shown in table VI especially among persons with serious defects as no dichromates arranged the chips correctly The type diagnosis was correct in 2/3 3/4 of the cases and thus the method is not infallible in this respect but seems well adapted for discriminating between the less serious cases of colour blindness where emplacement in an occupation requiring colour dis crimination would incur no risks and serious cases where occupation requiring no such discrimination seems advisable

Finally table VII shows the results of an examination of 232 colour blind subjects with Danish Standard 735 The test is inferior to the Farnsworth test

Table V

Misreadings of Hardy Rand and Rittler s pseudo isochromatic plates (AO H H R) (33 subjects)

	number	%
H R R showed red green defect	29	
not diagnosed (all of them deuteranomalous)	4	12
Number of subjects *deutan type*	21	
H R R showed deutan type	6	29
Number of subjects *protan type*	13	
H R R showed protan type	9	69
Number of examined anomalous trichromates (exclusive extr.)	13	
H R R showed mild defect	9	46
Number of examined dichromates	13	
H R R showed strong defect	6	50

half of them are found placed in the group with the highest score of errors (15 20) This means that individual count of mistakes cannot be used for a clinical indication of the seriousness of the defect of colour vision in the single case only estimates from large populations will show agreement between the number of errors and the seriousness of the defect

Tables III and IV show like data of 84 colour blind subjects using two Swedish plate sets It is only fair to note that the instructions for these plates plainly state that these are not constructed for the purpose of differentiated diagnoses The examinations with the Swedish plates show results agreeing with the count of errors using Japanese plates and one may suppose that

Table III
Misreadings of Bostrom Kugelberg (84 subjects)

	Deuter anomalous	Prot anomalous	Deuter anopia	Prot anopia	Extreme Deuter *anomalous*	Extreme Prot *anomalous*
0 errors	4					
1– 5 errors	6	2	1			
6–10 errors	8	1	3	2	1	
11–15 errors	19	8	16	6	4	3
total	37	11	20	8	5	3

Table IV
Misreadings of Bostrom II (84 subjects)

	Deuter anomalous	Prot anomalous	Deuter anopia	Prot anopia	Extreme Deuter anomalous	Extreme Prot anomalous
0 errors	3					
1– 5 errors	10	2	1			
6–10 errors	9	4	4	3	2	
11–15 errors	15	5	15	5	3	3
total	37	11	20	8	5	3

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H R R showed mild defect	9	46	
Number of examined dichromates	13		
H R R showed strong defect	6	50	

Table VI

Farnsworth Panel D 15 (59 subjects)

	total	%	
Incorrectly placed chips	26		
Correctly placed	33	56	
The 33 correctly placed diagnosed with Nagel as			
Deuteranomaly 19 out of 27			
Protanomaly 5 out of 6			
Deuteranopia 0			
Protanopia 0			
Extreme deuteranomaly 1 out of 5			
Extreme protanomaly 2 out of 4			
Unclassifiable 6 out of 8			
Number of incorrectly placed chips in the *deutan group*	16		
Deutan response in Farnsworth	12	75	
Number of incorrectly placed chips in the *protan group*	8		
Protan response in Farnsworth	5	63	

Table VII

Danish Standard 435 Colours for Labelling (232 subjects)

	total	%	
Number of examined anomalous trichromates	153		
misnaming of labelling colours	13	9	
Number of examined extreme anomalous trichromates	18		
misnaming of labelling colours	8	44	
Number of examined dichromates	61		
misnaming *of labelling colours*	50	83	

regarding selection of dichromates It must however be stressed that the standard test series is four times as large with corresponding possibilities of spread

in the data Considering the inexpensiveness of this test instrument it must be held a good assisting equipment to pseudo isochromatic plates a quick examination being made possible which can be made in any clinic and which can give an acceptable prognosis of fitness for occupation in 83 % of all cases of colour blindness

We are left with the question whether there is any safe clinical method which can decide whether a particular person is fit for a particular vocation exacting demands from the colour discrimination Till now one has perhaps attached too great importance to the type diagnosis that can be made with Nagel s anomaloscope disregarding the great variations within the groups established with this tool *The moot point is that the topic is never clearly analyzed This* is not only true of the many branches of industrial work variations also happen within the individual workshops of the same trade Also in the traffic sector a closer operational analysis of the absolute requirements to the colour vision which must be claimed because of safety is wanted

Summary

The historical evolution of the processes of investigation of the colour vision is reviewed *As many colour blind subjects can easily handle occupations claiming none too rigoristic* demands regarding discrimination of colour hues and saturation a distinction must be made between methods which can make certain whether or not the colour sense is normal and methods admitting of a qualitative evaluation of colour deficiency As an outcome of the present study it is shown that none of the pseudo isochromatic plates available *can be used* for a clear evaluation of the seriousness of the colour *deficiency No usable in*formations are obtained in this *respect through* count of misread plates In the *present investigation* the *American AO H H R plates* were found less adapted *for* an evaluation of type and seriousness and of the merits *suggested by the* makers of the plate regarding the diagnostic possibilities of the plates *these* could not be repeated *Farnsworth Panel D 15 proved to be the* best tool in occupational guidance of the subjects *examined* A simple naming of the colours of *Danish Standard Sheet for* labelling colours gave correct information regard*ing the degree of the defect in* more than 80 % *of the* cases

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THE OCULAR FUNCTION AND MOTILITY IN CONGENITAL BLEFAROPHIMOSIS

BY

JENS EDMUND

The term blefarophimosis refers to a condition in which there is a general diminution of the palpebral aperture in all its dimensions. In the congenital form which is always bilateral it may present itself with or without any other malformations. Apart from a peculiar form which occurs frequently among the japanese (30) three different types occur among caucasians.

1. Blefarophimosis without or with only slight ptosis but with a dystopia lateroversa of the inner angles and the puncta lacrymalia. This type which is inherited dominant through many generations (6 30) may be termed uncomplicated blefarophimosis.

2. Blefarophimosis associated with disturbed eye muscle function. In this type not only the levator muscle of the upper lid is disturbed resulting in a stiff ptosis but also other extrinsic eyemuscles may show an abnormal function. The anomaly which may show a dominant heredity (1 7 8 10 13 14 16 17 21 [illegible] [illegible] 27 29 30) may be termed complicated blefarophimosis.

3. Blefarophimosis associated with congenital malformations of the bulb (anophthalmus microphthalmus (24 30)) general developmental anomalies as

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Heredity

In 15 cases no heredity was found among the ancestors but in 2 cases (No 11 and No 25) siblings presented the same disease In the remaining 11 cases the disease was found among one of the ancestors and in all 11 cases the trait came from the father This autosomally dominant character showing male preponderance has been demonstrated by others (7 8 14 16 17 19 29 30) In a previous paper by the author (8) two families members of which are also included in this series (No 14 18 19 and 20) the same special type of heredity was found In all the mentioned 4 cases and the other 7 the trait reveals a dominant characteristic with male transmission passing directly from affected person to affected person without any skips or breaks in the continuity It has been demonstrated (29) that the ratio of affected to non affected is very high and that the father transmits the character 6 times as often as the mother (16 19 29 30) In all cases the malformation seems to be more severe in the offspring than in the ancestor and further the number of affected siblings seems to increase from generation to generation (7 8 10 14 22 29) While so far no case of transmission from the mother has been found in this series further progress of the malformation in the same family shows that the disease takes a more severe character in the affected females (22) That the affected female shows a more severe malformation might indicate that her general condition is also more deeply involved in a degenerative state This somehow confirms the assumption of Lenz (16) who as an explanation of the male preponderance of transmission suggested that the affected women are sterile or subfertile

The visual function and refraction

Vision was found normal in 8 cases Anisometropy *in 8 cases in all* of them due to anisoastigmatism 4 cases were myopic and in all 4 astigmatism was present *In 7 cases the* eyes were hypermetropic and in all these 7 cases esotropia *or esoforia* was present Ambiyopia was found in 9 cases and in only 1 case (No 25) it was not combined with squint.

In 6 cases astigmatism was not recorded because of the low age which made a reliable measurement impossible Out *of the* remaining 20 cases astigmatism was found in 14 and in all of them with an oblique axis This high incidence of astigmatism and further with an oblique axis may in some way be explained by the relation between the refractive state of the eye and the adaption of the eyelids to the bulb although probably the muscular dysfunction also plays an important role The characteristic lack of contact between the eye and the lids in this malformation must be assumed to be an important factor in this high occurrance of oblique astigmatism responsable for the extremely high incidence of visual dysfunction and ametropia as more than $^2/_3$ of the cases show anormal visual function

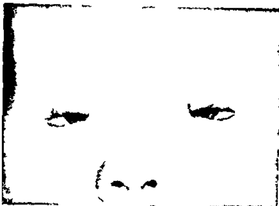


Figure 1
Congenital blefarophimosis of
he Waadenburg type II in a 8 year old child



Figure 2
Congenital blefarophimosis
of type I in a 15 year old male

1) A general diminusion of the palpebral *aperture* 2) *Enlarged distance between the* internal canthi often amounting to the double of the length of the palpebral fissure 3) Flat nasal bridge 4) Stiff ptosis with immobility of the eye lids 5) Lack of tarsal fold due to lack of function of the levator superior muscle 6) Overaction of the M frontalis 7) The eyelids *defectively developed with thin smooth atrophic* skin and flexible tarsal plate 8) Irregular growing eyelashes irregularly appearing in a greater or lesser distance from the margo palpebrae superior 9) Dystopia lateroversa of the puncta lacrymalia 10) *Elongatio canaliculi lacrymalia 11) A* peciar boatshaped outli e of the palpebral aperture with lack of contact between the bulb and the lid

proportionate dwarfism or mongolism (10 24 30) combined with congenital cardiopathy (10 24) or as a part of Waardenburg or van den Bosch syndromes (30)

This paper deals only with the two first mentioned types The clinical characteristics which has been pointed out by Waardenburg (30) and others (5 6 8 14 19 29) are presented and described in figure 1 and 2 Besides these developmental *malformations however some functional defects of the eye and* its adnexa are associated *with the complicated type of this syndrome and* based *on a study of the clinical pattern and function of the eyes it* is the aim of this paper to point out the relation between the visual function the ocular motility and ptosis in congenital blefarophimosis

Material

The series includes 26 cases all observed in the department of ophthalmology Rigshospitalet Copenhagen The clinical data have been summarized in table I

In the following the 11 different groups will be discussed seperately

12 404/56	13 121/66 67	14 772/6	15 366/67-68	16 418/68	17 15/64 65	18 631/55	19 408/56	20 605/55	21 750/62 63	22 288/63 64	23 63/65 66	24 579/59	25 17/69	26 2683/68 69	Total
									+	+		+			13
	O		O	O							+			+	11
															0
+		+			+	+	+	+							3
						+	+	+							4
		+				+	+	+					+		2
			+										+	+	8
		+		+	+										8
							+					+			4
+	+					+		+	+	+	+				7
			O								O				6
															0
+		+			+		+		+	+		+	+	+	14
			+											+	13
+	+			+		+	+	+	+	+	+	+		(+)	11
		+			+										2
													+	+	2
+		+	O	+	O	+	+	+	O	O	+	+	+	O	9
															0
															0
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	26
															4
														(+)	2
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
+	+	+	+		+		+		+		+	+	+	+	22
				+		+		+		+					4
O	O	O	O	O	O	+	O	+	(+)	+	+	+	O	O	6
+		+	+		+	+	+	+	(+)	+	+	+	+	+	20
O	O	(+)	+	+	+	+	+	+	+	+	+	+	+	+	13

Table 1
(continued)

ally withdrawn from the eyeball Further enlarged interocular distance and lengthened horisontal canaliculi

This however does not imply that they all take same course of development during growth As it has been mentioned above the malformation seems to be more severe in the offspring than in the ancestor which means that the sporadic cases may take a milder form than the familial cases This can be demonstrated from this series It appears from table 1 that abnormal ocular *function and* motility occur far more often among the cases with a hereditary trait than among the sporadic cases This observation is illustrated by figure 3 and 4 In figure 3 the same case (No 1) is shown at the age of 5 and 15 years It will

Case no	1 373/60	2 877/61	3 554/61 62	4 224/64 65	5 653/58	6 248/67-68	7 1257/67 68	8 614/67 68	9 538/67-68	10 734/65 68	11 112/26
Heredity	O	O	O	O	O			O	O		
Father						+	+			+	
Mother											
Brother											
Si ter											
Sibling											+
Vision											
normal	+		+		+		+	+	+		+
anisometropy		+		+						+	
myopia		+				+					
hypermetropia											
Astigmatism	O		O					O			O
regular											
oblique		+		+	+	+				+	
Primary Position											
parallel	+	+	+	+	+	+	+	+	+	+	+
convergence											
divergence											
heterophoria											
Amblyopia	O	O	O	O	O	O	O	O	O	O	O
Function of musc levator											
normal											
reduced											
missing	+	+	+	+	+	+	+	+	+	+	+
Supraduction											
normal	+	+	+	+							
reduced					+						
missing						+	+	+	+	+	+
Horisontal movements											
normal	+	+	+	+	+	+	+	+	+	+	+
abnormal											
Nystagmus	O	O	O	O	O	O	O	O	O	O	O
Bell s phenomenon											
normal			+	+	+	+		+	+	+	+
abnormal											
Change in the palpebral aperture by horisontal eye movements	O	O	O	O	O	O	O	O	O	O	O

Table 1

The clinical data and observations in 26 cases of congenital blefarophimosis presented in 11 subgroups

The remaining 7 groups all deal with the function of the extraocular motility including the levator palpebrae muscle

The ocular and extraocular motility

The function of the levator palpebrae superioris was missing in all 26 cases which means that all cases represent the type of blefarophimosis with stiff ptosis as decribed by Waardenburg (30) This special type of blefarophimosis includes 3 symptoms 1) hypoplasia of the caruncle and semilunar fold 2) stiff taut lids small in their transverse and vertical dimensions and 3) dysplastic flexible tarsi the lower lids drooping lateraly downwards and there occasion

12 404/6	13 121/66 67	14 772/58	15 365/67 68	16 418/68	17 15/64 65	18 631/55	19 408/56	20 605/55	21 750/62 63	22 288/63 64	23 61/65 66	24 579/59	25 17/68	26 2683/68 69	Total
									+	+		+			13
	O		O	O							+			+	11
+		+			+	+	+	+							0
															3
						+	+	+							4
		+				+	+	+					+		2
			+										+	+	8
		+		+	+										8
							+					+			4
+	+					+		+	+	+	+				7
			O								O				6
															0
+		+			+		+		+	+		+	+	+	14
			+											+	13
+	+			+		+	+	+	+	+	+	+		(+)	11
		+			+										2
													+	+	2
+		+	O	+	O	+	+	+	O	O	+	+	+	O	9
															0
															0
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	26
															4
														(+)	2
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
+	+	+	+		+		+		+		+	+	+	+	22
				+		+		+		+					4
O	O	O	O	O	O	+	O	+	(+)	+	+	+	O	O	6
+		+	+		+	+	+	+	(+)	+	+	+	+	+	20
O	O	(+)	+	+	+	+	+	+	+	+	+	+	+	+	13

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Heredity	O	O	O	O	O			O	O		
Father						+	+			+	
Mother											
Brother											
Sister											
Sibling											+
Vision											
normal	+		+		+		+	+	+		+
anisometropy		+		+						+	
myopia		+				+					
hypermetropia											
Astigmatism	O		O					O			O
regular											
oblique		+		+	+	+				+	
Primary Position											
parallel	+	+	+	+	+	+	+	+	+	+	+
convergence											
divergence											
heterophoria											
Amblyopia	O	O	O	O	O	O	O	O	O	O	O
Function of musc levator											
normal											
reduced											
missing	+	+	+	+	+	+	+	+	+	+	+
Supraduction											
normal	+	+	+	+							
reduced					+						
missing						+	+	+	+	+	+
Horisontal movements											
normal	+	+	+	+	+	+	+	+	+	+	+
abnormal											
Nystagmus	O	O	O	O	O	O	O	O	O	O	O
Bell s phenomenon											
normal			+	+	+	+		+	+	+	+
abnormal											
Change in the palpebral aperture by horisontal eye movements	O	O	O	O	O	O	O	O	O	O	O

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lift the lid on direct galvanic stimulation (13) and by histological examination of a case with disturbed upward movement of the lids in which atrophy of the levator muscle and hypoplasi[1] of the superior recti muscles were demonstrated but with normal oculomotor trochlear and abducens nuclei (3) Many surgeons (1 4 17 19 22) have confirmed that only very few traces of the levator muscle can be found during surgical treatment The consequence of this lack of function of the M levator palpebrae will be discussed further in connection with the dysfunction of other extraocular muscles

The primary position of the eyes was normal parallel in 13 cases although one case No 25 like case No 26 revealed esoforia Exotropia was found in 2 cases 1 of them case No 17 had a divergence of the exo A type without amblyopia but showing an alternating suppression The other case No 14 presented a high grade anisometropy being hypermetropic on the right eye myopic on the left eye with oblique astigmatism on both eyes and amblyopia on the left eye Esotropia was found in 10 cases and esoforia further in 2 cases In 7 out of the 10 cases with primary convergence amblyopia was present In 1 case No 15 amblyopia was impossible to test because of the low age and in the 2 remaining cases No 21 and 22 an alternating suppression was found

The horisontal movements were normal in 22 cases In four cases No 16 18 20 and 22 abduction seem to be reduced and in 3 out of these nystagmus occurred in the abducted eye This reduction of abduction was only present in versional movements by monocular movements no paralysis or retraction was found in any case Nystagmus was present in 6 cases all of them with convergent squint in 4 of them further with amblyopia The effect of the abnormal position and horisontal movements of the eyes will be discussed further below

The vertical eye muscle function

Disturbed upwards movements of the eyeball in combination with ptosis due to reduced function of the superior recti muscle have been recorded by several authors (? 3 4 9 14 15 17 19 21 2? 24 26 27 ?8 29 30) and has also been observed associated with congenital blefarophimosis (14 19 30)

The supraduction was found normal in 4 cases all of them showing normal motility of both eyes reduced in 1 case but with normal horisontal motility and missing in 21 cases In 1 of these case No 26 reduced action of supraduction was found on 1 eye (+) All cases presented overaction of the M frontalis

Bell s phenomenon

This well known phenomenon consists of an upward rolling of the eyes when forcible efforts are made to close the eyelids against resistance (11 12) (Fig 5) ?1 cases were examined for this reflex and in only 1 case No 22 the phenomenon was missing Usually this reflex movement is thought to be due to action

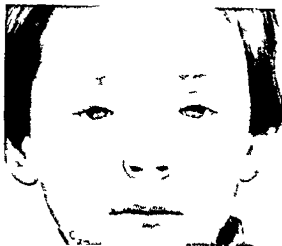



Figure 3
Congenital blefarophimosis of the type I in which the palpebral aperture has grown to an almost normal size and appearance

be seen that the palpebral aperture has grown to an almost normal size and that the general appearance is close to the normal Figure 4 demonstrates a case with a dominant hereditary trait (No 20) at the age of 5 and 27 years It appears that practically all the characteristic features of blefarophimosis are present and that the palpebral aperture is almost unchanged in size

Based on the presence of a positive Koster sign*) Braun (5) attributes the ptosis to aplasia of the levator muscle This view is supported by the failure to




Figure 4
Congenital blefarophimosis of the Waardenburg type II

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*) Koster (15) stresses the fact that the fibres of the superior tarsal muscle adhere to the tendon of the M levator palpebrae Koster sign = lack of reaction of the upper lid on cocaine due to absence of the M levator palpebrae superior



Figure 6

Change in the palpebral aperture by horisontal eyemovements B showing equal palpebral apertures in primary position with binocular vision A and C showing the change in the size of the aperture being enlarged in abduction and diminished in adduction

Change in the palpebral aperture by horisontal eyemovements

In 13 cases that is half of the series a change in the size of the palpebral aperture was noticed by horisontal eyemovements the aperture being enlarged in the abducted eye and diminished in the adducted eye (Fig 6) Similar synchinetic movements has been observed in the Turck Stilling Duane syndrome in which there is a greater or lesser restriction on abduction retraction of the defective eye stricture of the palpebral fissure on adduction dilatation of the palpebral fissure and protrusion of the globe on intended abduction of the defective eye (18 25 30 31) As mentioned above in blefarophimosis no paralysis of the horisontal muscles has been noticed and no retraction of the adducted eye observed The enlargement of the palpebral aperture in the abducted eye is not due to any function of the levator muscle but is mediated by an overaction of the musculus frontalis This phenomenon of overaction seems to be associated with the fixation of the eye and the eye of fixation In 12 out of the 13 cases showing this phenomenon a squint was present The 13th case No 25 did not present a squint but had an amblyopia on the right eye which means that this eye might have been squinting in the childhood This means that all of the cases showing change in the palpebral aperture by horisontal eye movements had an abnormal binocularity All except one case No 15 had visual dysfunction or refractive errors in one or both eyes

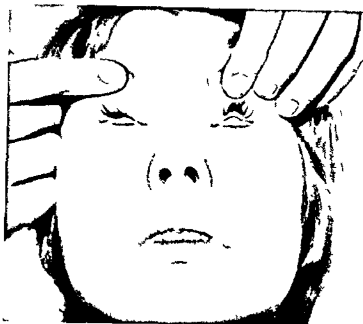
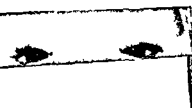
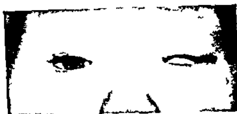


Figure 5
Bell s phenomenon in case No 21 with lack of function of the M recti superiores

in the M superior rectus (31) but in all cases with normal Bell s phenomenon the function of the superior recti muscles were lacking The presence of Bell s phenomenon in individuals who cannot voluntarily elevate their eyes is supposed to indicate a supranuclear lesion (31) As mentioned above however certain findings (1 3 5 15 17 26 27) seem to indicate that the most plausible hypothesis of the muscular dysfunction seems to be that there are primary disturbances of the differentiation of the muscles that elevate the eyelids According to Waardenburg (30) nuclear aplasias or dysplasias inhibiting the development of the neuromusclar unit do not cause secundary dysplasias of independantly formed muscles Consequently abscense or dysplasia of eye muscles should be viewed as a local myogenic developmental anomaly independant of the central nervous system The stiff ptosis thus demonstrates one typical example of a malfunction which cannot be explained by nervous degeneration

If this holds true the presence of a normal Bell s phenomenon in all thes cases with lack of function of the superior rectus muscle points to another explanation The reflex movement is not due to the rectus superior muscle but to the inferior oblique muscle This assumption is confirmed by case No 22 in which the Bell s phenomenon was normal on the right eye but missing on the left eye on which there was a paresis of the inferior oblique muscle This finding further supports Waardenburg s hypothesis that the syndrome is a myogenic rather than a neurogenic dysplasia





igure 9
cover test
tion B After cover test squinting of the left
of the palpebral aperture

llustrates this explanation The eyes are
he head is turned backwards When the
onverges and the left lid aperture closes
only present when the eyes are turned
tain this situation When the body height
when the head is held in normal position
r necessary
ion and the fixation of the eye is further
d operation for esotropia had been per
it at the age of 13 vision was 6/6 on both
rimary position was parallel and in this
stereopsis for large objects (Fig 11)

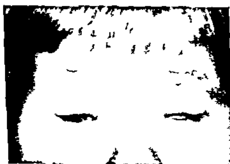


Figure 10
The relation between the head posture and the palpebral apertures
A The head reflected backwards binocular vision, palpebral apertures equal.
B The head turned to an erect position fixation with the right eye while the left eye closes

ERRATUM

Course in Retinal Detachment
announced in Acta Ophthalmologica vol 48 fasc 6 1970 page 1207 The course takes place on *June 3 4 and 5 1971* and not on May 20 21 and 22 1971



Figure 7
Diminished palpebral aperture on the squinting right eye

In the primary position with fixation on the far point both palpebral apertures were equal in all of the cases In cases with esotropia the aperture on the squinting eye was smaller (Fig 7) On versional movements fixation is done by the abducting eye the adducted eye converges and the lid aperture closes (Fig 8) The same thing happens if the binocular fixation is broken in primary position e g by a cover test of the squinting eye (Fig 9) This can only mean that the overaction of the M frontalis is mediated by the visual reflex

The importance of vision and binocular vision is further illustrated by the head posture Some of the children with congenital blefarophimosis turn their head backwards a head posture usually explained by the ptosis That the ptosis is a less important factor in the backward turn of the head is seen by the facts that in the first place not all of them make this backwards turn and in the second place that it disappears with growth Probably it is neither the ptosis nor the lack of supraduction that causes the phenomenon as not all patients with lack of supraduction make this head turn As it will be seen from the following it seems more likely that it is due to lack of binocular vision in pri



Figure 8
Enlargement of the eye of fixation (right eye) diminishing aperture on the non fixation eye in adduction (left eye)

a connection seems to exist between convergent squint and ptosis on the squinting eye Further the position of the eyelid during the act of fixation of the eye points to a close connection between the visual reflex and the size of the palpebral aperture

Concluding remarks and summary

In 26 cases of congenital blefarophimosis of the Waardenburg type with stiff ptosis a hereditary trait was found in 11 cases in all of them with autosomally dominant male transmission In the 15 cases without any heredity the disease was found to be less severe than in the hereditary cases Visual dysfunction was found in more than ²/₃ of the cases and an extremely high incidence of astigmatism with oblique axis was found probably due partly to the muscular dysfunction partly to the lack of adaption between the eyelids and the bulb

Heterotropia was present in 12 cases being exotropic in 2 and esotropic in 10 cases Reduced function of the M superior recti was present in 21 cases all of them with normal horisontal movements of the eye

Bell s phenomenon was normal in 20 cases all of them without function of the M rectus superior It is assumed that the Bell s phenomenon is due to the inferior oblique muscle as the only case in which the phenomenon was missing showed a paralysis of the inferior oblique muscle

The size of the palpebral aperture i e the degree of ptosis was found to be maintained by the state of action of M frontalis and to be related to the position and the movements of the eyes assumingly depending on the visual function

In a normal primary position with binocular bifoveal vision both apertures were of equal size If this visual condition is disturbed either by a cover test resulting in monocular squint or by horisontal eye movements *in which* the binocular fixation is broken the palpebral aperture on the non fixating eye diminishes while the aperture of the fixating eye enlarges due to an over action of the M frontalis

The effort to obtain binocular *vision is* further suggested as an explanation of the backward reflexion of the head in childhood that disappears with growth

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Figure 11
The primary position with correcting spectacles in case No 21

In monocular eyemovements the palpebral aperture is 2 mm in adduction and 7 mm in abduction (Fig 6) equal on both sides The same effect is seen in binocular movements When the patient fixates the far point and is binocular the two palpebral apertures are equal If the binocular state is broken by means of a cover test of the left eye the eye converges and the aperture diminishes (Fig 12 A) If the patient performes an active convergence that means by fixation of a light approaching the eye both eyes converges and in contrast to the above the apertures remain equal because the patient is bifoveal during the converging process (Fig 12 B)

Synkinetic movements associated with congenital ptosis has been observed before but always associated with some paralysis of abduction or other retraction syndromes (2 9 18 20 23 25) Ptosis as a function of vertical muscle anomalies has also been observed and the importance of correction of the vertical squint before ptosis operation stressed as the ptosis almost disappeared following operation for squint (4 28)

The observations reported in 13 cases of this series support the view that



Figure 12
The size of the palpebral aperture following cover test (A) and active convergence (B)

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around the optic nerve. The spokesmen of this theory are in particular *White*[9] (1895), *Liebrecht*[7] (1906), *Doubler & Marlow*[5] (1917) and *Symonds*[17] (1924).

In the second theory the explanation of the aetiology is that bleeding from the subarachnoid space is forced into the subarachnoid space of the optic sheath where it causes by compression of the central retinal vein and of the venous choroid anastomoses at the lamina cribrosa severe congestion of the retinal veins which burst and thus cause retinal haemorrhages. The presupposition of this theory as of the first one is the existence of free communication between the intracranial and intraorbital subarachnoid space. This theory has been propounded by *Paton*[14] (1924), *Riddoch & Goulden*[15] (1925), *MacDonald*[9] (1931), *Miller & Cuttino*[1] (1948) and in particular by *Manschot & Hampe*[10] (1950) and *Manschot*[11] (1954).

The main principle of the third theory is that the acute intracranial subarachnoid haemorrhage is accompanied by a marked increase in intracranial presure including a highly increased venous pressure which is transmitted to the retinal veins by way of the venous circulation of the eye. The marked venous congestion causes venous rupture in the retina in the optic sheath and in the orbital tissue. In this theory of course there is no presupposition of a free communication between the intracranial and orbital subarachnoid spaces. This theory is supported by *Ballantyne*[2] (1943), *Walsh & Hedges*[18] (1951), *Hedges & Walsh*[8] (1955), *Bisland & Topilow*[3] (1959), *Cordes*[4] (1953), *Smith Kearns & Sayre*[16] (1957), *Weaver & Davis*[19] (1961) and *Morris & Henkind*[13] (1967).

Present Cases

Through the 8 year period from April 1st 1959 to March 31th 1967 the Neurosurgical Department S of the Århus Municipal Hospital admitted 378 patients with intracranial subarachnoidhaemorrhage without co existing haematological or other systemic diseases. All these patients exhibited a typical clinical syndrome of acute headache and neck rigidity, many had impaired consciousness and several had neurological signs, in most cases hemiparesis. All the patients were examined by a neurosurgeon and all except a few of the most debilitated ones who died soon after admission were examined repeatedly by an ophthalmologist. Of the 378 patients 177 were males and 151 females. The material may be divided into 4 clinical groups, there being 154 with ruptured sacculated aneurysms, 43 suspected of sacculated aneurysms, 31 with plexiform angiomas and 100 with haemorrhagic apoplexy.

The diagnoses of ruptured sacculated aneurysm and plexiform angioma were in all cases confirmed by cerebralangiography and at operation or autopsy. 12 patients had multiple aneurysms. In 11 of these cases there is no doubt as to

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From Neurosurgical Department S, Municipal Hospital, Århus (Heads: Jens H. Rasmussen and Verner Knudsen) and Ophthalmic Pathology Laboratory, University of Copenhagen (Head: S. Ry Andersen)

INTRAOCULAR HAEMORRHAGE FOLLOWING SUBARACHNOID HAEMORRHAGE

BY

J. A. FAHMY, V. KNUDSEN and S. RY ANDERSEN

In the course of the past 18 months 5 patients with vitreous haemorrhage arising in connection with subarachnoid haemorrhage from ruptured sacculated aneurysms have been admitted to Neurosurgical Department S of the Municipal Hospital, Århus. Three of the patients died and after the autopsy the eyes were studied histologically (1). These cases aroused our interest in the aetiology and prognostic role of fundus haemorrhages in subarachnoid haemorrhage.

We therefore perused the literature in a search for an aetiological theory. Thereafter we studied in retrospect whether the clinical data correspond to the theories advanced.

In 1881 *Litten*[8] reported apparently as the first on a relationship between fundal and sabarachnoid haemorrhage. Since then numerous authors have discussed theories concerning the aetiology of fundus haemorrhages caused by subarachnoid haemorrhage. At present there are 3 main theories which have been modified in various ways by the different authors.

The first theory is that blood from the subarachnoid space forces its way through the optic sheath to the lamina cribrosa, whence it diffuses by way of the perivascular spaces or breaks through direct to the retina and possibly to the vitreous. The presupposition of this theory is free communication between the intracranial subarachnoid space and the intraorbital subarachnoid space

around the optic nerve The spokesmen of this theory are in particular *White*[6] (1895) *Liebrecht*[7] (1906) *Doubler & Marlow*[5] (1917) and *Symonds*[17] (1924)

In the second theory the explanation of the aetiology is that bleeding from the subarachnoid space is forced into the subarachnoid space of the optic sheath where it causes by compression of the central retinal vein and of the venous choroid anastomoses at the lamina cribrosa severe congestion of the retinal veins which burst and thus cause retinal haemorrhages The presupposition of this theory as of the first one is the existence of free communication between the intracranial and intraorbital subarachnoid space This theory has been propounded by *Paton*[14] (1924) *Piddoch & Goulden*[15] (1925) *MacDonald*[9] (1931) *Miller & Cuttino*[12] (1948) and in particular by *Manschot & Hampe*[10] (1950) and *Manschot*[11] (1954)

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The diagnoses of ruptured sacculated aneurysm and plexiform angioma were in all cases confirmed by cerebralangiography and at operation or autopsy 12 patients had multiple aneurysms In 11 of these cases there is no doubt as to

which aneurysm ruptured and in the tables these patients are listed by the ruptured aneurysm In one case autopsy revealed rupture of an aneurysm of the anterior communicating artery as well as large haemorrhage in the region of the chiasm and at the same time there was a smaller haematoma corresponding to a ruptured aneurysm of the middle cerebral artery This patient is listed as *aneurysm of the anterior communicating artery*

A diagnosis of haemorrhagic apoplexy was made in patients who had spontaneous intracerebral haematomas not arising from an aneurysm or angioma The diagnosis was confirmed by cerebral angiography and ventriculography operation or autopsy

On the other hand the diagnosis suspected aneurysm is a purely clinical one although in several of these cases there was a predominant likelihood of aneurysms which only could not be confirmed

Cerebral angiography was done on *309* of the *328* patients *19* were so debilitated that they died soon after admission without having had angiography

In 172 patients lumbar puncture yielded haemorrhagic spinal fluid with xanthochromia and in 138 out of the 198 operated cases the operation report contains definite information about subarachnoid haemorrhage 137 patients died and of them 114 were autopsied In 269 the subarachnoid haemorrhage could be confirmed without a doubt while in 59 it could not be definitely confirmed according to the data at hand However among these patients a number underwent operation for *ruptured sacculated aneurysms or angiomas 14 out of* 59 had neither lumbar puncture operation nor autopsy either because they died soon after admission and autopsy was not allowed or because their symptoms and signs were so vague that there was no indication for further studies. All 14 are listed as suspected of aneurysm

Table 1 gives a clinical analysis of the fundus haemorrhages in respect to diagnosis to whether the haemorrhage was unilateral or bilateral and to whether a shoked disc co existed with fundus haemorrhage

It will be seen that 73 out of the 328 patients (22 2 %) had had fundus haemorrhage while only 32 (9 8 %) had choked disc There were 38/73 (52 %) unilateral fundus haemorrhages but frequently not on the side of the intracranial haemorrhage

We attempted a rough quantitative and qualitative classification of the fundus haemorrhages in respect to shape degree and site In 14 patients the haemorrhages were preretinal and of this group 10 had vitreous haemorrhage All the patients with preretinal haemorrhages exhibited a typical history of ruptured sacculated aneurysms but 2 patients died soon after admission *without* having had angiography and autopsy was not allowed both are listed as suspected of aneurysm In the 59 patients with retinal haemorrhages 30 had *streaked haemorrhages* while 24 had flat flame shaped haemorrhages and 5 had both flat and streaked haemorrhages

Table 1

Incidence of fundus haemorrhage

		Fundus haemorrhage			Choked disc / fundus haemorrhage		
		bilateral	unilateral	total	bilateral	unilateral	total
Ruptured sacculated aneurysm	154	21	29	50	15/13	5/3	20/16
Suspicion of aneurysm	43	1	4	5	1/1	2/1	3/2
Plexiform angioma	31	2	2	4	3/2	1/1	4/3
Haemorrhagic apoplexy	100	11	3	14	5/[illegible]	0/0	5/2
Total	3 8	35	38	73	24/18	8/5	32/23

26 out of the retinal haemorrhages had to be characterized as mild 32 as moderately severe and 15 as severe All 14 preretinal haemorrhages were severe One patient with retinitis pigmentosa also had severe flat retinal haemorrhages but this bleeding was absorbed Only 4 patients with preretinal haemorrhages survived all four had vitreous haemorrhage as well

Among the 23 patients with co existing choked disc and retinal haemorrhage there was no special characteristic type of haemorrhage the bleeding being streaked as well as flat mild as well as severe It is difficult to classify the haemorrhages by site 6 were predominantly of a papillary site 25 predominantly peripapillary and 28 peripheral but several were peripapillary as well as peripheral There were no special characteristics in respect to shape and severity in the different sites

In Table 2 the Material is analysed with a view to impairment of consciousness and neck rigidity as well as incidence of co existing retinal haemorrhage As will be seen 2°7 patients were initially unconscious while only 140 had initial neck rigidity Many did not develop neck rigidity until hours after the onset of the disease and several patients were deeply unconscious but had no neck rigidity It is an interesting feature of this table that retinal haemorrhage within the group of ruptured sacculated aneurysms was most common in pa

which aneurysm ruptured, and in the tables these patients are listed by the ruptured aneurysm In one case autopsy revealed rupture of an aneurysm of the anterior communicating artery as well as large haemorrhage in the region of the chiasm and at the same time there was a smaller haematoma corresponding to a ruptured aneurysm of the middle cerebral artery This patient is listed as aneurysm of the anterior communicating artery

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Table 3
Incidence of fundus haemorrhage and intracerebral haematoma in ruptured sacculated aneurysms

		Retinal haemorrhage	Preretinal haemorrhage	Co existing intracerebral haematoma
Anterior cerebral artery	8	2	0	4
Anterior c mmunicating artery	47	13	6	11
Carotid artery	56	12	5	8
Middle cerebral artery	39	11	0	19
Basilar artery	4	0	1	0
T tal	154	38	1?	4?

a whole Preretinal haemorrhage was never present among the healthy sur vivors but in 4 of the 40 disabled survivors and in 8 of the 75 fatal cases Choked discs appear to play less prognostic role Within the entire series choked discs were present in 7 3 % of the healthy survivors in 7 4 % of the disabled survivors and in 13 % of the fatal cases

Discussion

When the clinical findings are compared with the three theories on the aetio logy of fundus haemorrhage it is difficult to say which theory is most correct. However it is striking that retinal haemorrhages were most common in the presence of subarachnoid haemorrhages arising from ruptured aneurysms (3 5 %) while fewer retinal haemorrhages were found in patients with haemor

Table 2

Incidence of fundus haemorrhage compared with initial unconsciousness and neck rigidity

		Unconsciousness / fundus haemorrhage			Neck rigidity / fundus haemorrhage		
		More than 24 hours	Less than 24 hours	None	Severe	Mild	None
Ruptured sacculated aneurysm	154	25/12	92/28	37/10	4[illegible]/19	38/[illegible]	69 [illegible]4
Suspicion of aneurysm	48	2/1	11/1	30/3	9 2	4/1	30 [illegible]
Plexiform angioma	31	6/2	11/1	14/1	6/1	5/2	[illegible]0/1
Haemorrhagic apoplexy	100	37/8	43/4	20/2	15/1	16 2	69 11
Total	328	[illegible]0 23	15[illegible]/[illegible]4	101/16	[illegible]/23	63/12	188/35

tients with severe initial neck rigidity and with long initial unconsciousness This indicates a relationship between the severity of the haemorrhage and the incidence of retinal haemorrhage

Table 3 gives a more detailed analysis of the group with ruptured sacculated aneurysms It is apparent that retinal haemorrhage was most common in the presence of ruptured aneurysms from the internal carotid and the anterior communicating arteries where the bleeding is into the free subaranoid space while intracerebral haematomas were more common where the bleeding issued from the middle or anterior cerebral artery

Lastly Table 4 sets out the prognostic role of the retinal haemorrhages and choked discs It will be seen that the prognosis is poorer in the presence of retinal haemorrhage or choked disc Among 96 healthy survivors only 9 had retinal haemorrhage (9 3 %) among 94 disabled survivors 18 had retinal haemorrhage (19 1 %) while among the 138 fatal cases 46 had retinal haemorrhage (33 3 %)

The same finding is made in the group of ruptured sacculated aneurysms Among healthy survivors 15 % (6/39) had retinal haemorrhages among disabled survivors 30 % (12/40) and among the fatal cases 43 % (32/75) had retinal haemorrhages In other words this is as striking as for the material as

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Total	154	38	12	42

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Table 4
Prognostic significance of fundus haemorrhage and choked disc

		Healthy survivors			Disabled survivors			Fatal cases		
			Fundus haemorrhage	Choked disc		Fundus haemorrhage	Choked disc		Fundus haemorrhage	Choked disc
Ruptured sacculated aneurysm	154	39	6	5	40	12	1	75	32	14
Suspicion of aneurysm	43	33	2	1	7	1	1	3	2	1
Plexiform angioma	31	12	1	1	15	2	2	4	1	1
Haemorrhagic apoplexy	100	12	0	0	32	3	3	56	11	2
Total	328	96	9	7	94	18	7	138	46	18

rhagic apoplexy (14 %) although the latter nearly always have considerably larger intracerebral haematomas and smaller subarachnoid haemorrhages than patients with aneurysmal haemorrhage Correspondingly it may be seen from Table 9 that only 31 % of the patients with haemorrhagic apoplexy had neck rigidity while this was present in 55 % of the patients with ruptured aneurysms The initial intracranial pressure in the aneurysmal haemorrhages is not known with certainty but often the bleeding is sparse and the loss of consciousness due rather to spasms in the arteries than to an initially high intracranial pressure

It is markable that fundus haemorrhages were more common in the presence of ruptured aneurysms from the internal carotid and the anterior communicating arteries where the bleeding i into the free subarachnoid space than in ruptured aneurysms from the middle and anterior cerebral arteries where the bleeding usually is into the cerebral tissue which more often gives rise to intracerebral haematomas (cf Table 3) In the same way it is remarkable that the 11 preretinal haemorrhages were from aneurysms of the carotid and anterior communicating arteries while no preretinal haemorrhages were found in aneurysms of the middle and anterior cerebral arteries

This militates against the fundus haemorrhages being due exclusively to an initially high intracranial pressure (Ballantyne 1943)

Only 20 out of the 154 patients with subarachnoid haemorrhages from ruptured aneurysms had choked discs invariably of mild degree 1 2 dioptres This is peculiar as it may be expected that absorption of cerebrospinal fluid from the subarachnoid space is reduced after the severe subarachnoid haemorrhages Indeed a few of the patients developed hydrocephalus

The histopathological studies done so far on 8 eyes from 4 patients with ruptured aneurysms definitely exclude the theory that the haemorrhages from the optic sheath break through the lamina cribrosa[1] The second theory that the retinal haemorrhages are due to congestion of the central vein and of the choroid venous anastomoses also seems unable to explain the retinal haemorrhages in all cases although it is supported by the fact that the incidence of retinal haemorrhages was higher in the presence of bleeding into the free subarachnoid space

It might be imagined that further information was obtainable by studying other groups of acute neurosurgical cases with an initially high intracranial pressure e g patients with cerebral infarction following emboli with acute subdural and extradural haematomas and other groups In the near future it may be anticipated that continuous measurement of the intracranial pressure in acute neurosurgical cases will come into common use This will afford a possibility of further studies even though patients with ruptured sacculated aneurysms do not reach the neurosurgical departments until hours after the initial haemorrhage

We are planning to perform further ophthalmohistopathological studies on patients who have died of subarachnoid haemorrhages and hope to be able to publish a paper on this subject in the near future

Summary

The three main theories on the aetiology of fundus haemorrhages in intracranial subarachnoid haemorrhage are briefly described A clinical retrospective study of 328 patients admitted with subarachnoid haemorrhage to the Neurosurgical Department S of the Arhus Municipal Hospital during the period 1st April 1959 to 31st March 1967 is reported The patients are divided into 4 diagnostic groups sacculated aneurysm suspicion of aneurysm plexiform angioma and haemorrhagic apoplexy The diagnosis suspicion of aneurysm is clinical while the other 3 groups were confirmed by angiography and operation or autopsy The incidence of fundal haemorrhages in the various diagnostic groups is reported, the group sacculated aneurysm being subdivided by site of aneurysm

Fundus haemorrhage was found in 73 out of 328 patients (22 2 %) The haemorrhage was most common in patients with aneurysm of the anterior communicating artery (40 0 %) In most cases the haemorrhage was unilateral (52 0 %) Moreover the highest incidence of fundus haemorrhage was found in patients with neck rigidity and in patients in whom the initial unconsciousness exceeded 24 hours It is clearly apparent that the prognosis was poorest for patients having fundus haemorrhages

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COLOBOMA OF EYELID AND HARELIP

A case report

BY

HANS FLEDELIUS

Coloboma of the eyelid has a low incidence while harelip is one of the most common congenital defects The combination of the two is only seldomly reported and then as part of more complex entities Our report however deals with a case where the two defects occur together in a newborn with no evidence of other malformations

The patient a girl was born on the 8th of Sept 1968 in the Department of Obstetrics A Rigshospitalet Copenhagen The delivery was precipitated with oxytocin but otherwise uncomplicated The weight at birth was 2650 grammes Two defects were obvious

1) A partial harelip on the left side Cleft palate or other oral defects were not present External ear normal on both sides

2) A coloboma of the left upper eyelid As shown on the pictures the rectangular defect involves all the structures of the medial half of the lid including tarsal plate and eyelashes The gap is limited by slightly rolled conjunctival edges medially and laterally Upwards the conjunctiva of the lid fuses with the bulbar conjunctiva a few millimeters behind the cutaneo conjunctival transition in the upper boundary of the defect Thus the upper fornix is almost obliterated in the coloboma area In relaxed sleep there is partial exposure of the cornea and sclera while exposure does not exist when forcefully crying



Fig 1a
The girl in normal sleep

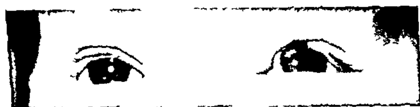


Fig 1b
The girl awake

The cornea iris lens and fundus picture are normal on both sides The lacrimal pathways also normal

There were no evidence for luetic or toxoplasmotic infection and no evidence for other external or internal developmental defects The chromosome pattern was normal female without trisomy or other abnormalities

HOLGER EHLERS
ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the University Departments of Ophthalmology
(Head Holger Ehlers)
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COLOBOMA OF EYELID AND HARELIP

A case report

BY

HANS FLEDELIUS

Coloboma of the eyelid has a low incidence while harelip is one of the most common congenital defects The combination of the two is only seldomly reported and then as part of more complex entities Our report however deals with a case where the two defects occur together in a newborn with no evidence of other malformations

The patient a girl was born on the 8th of Sept 1968 in the Department of Obstetrics A Rigshospitalet Copenhagen The delivery was precipitated with oxytocin but otherwise uncomplicated The weight at birth was 2650 grammes Two defects were obvious

1) A partial harelip on the left side Cleft palate or other oral defects were not present External ear normal on both sides

2) A coloboma of the left upper eyelid As shown on the pictures the rectangular defect involves all the structures of the medial half of the lid including tarsal plate and eyelashes The gap is limited by slightly rolled conjunctival edges medially and laterally Upwards the conjunctiva of the lid fuses with the bulbar conjunctiva a few millimeters behind the cutaneo conjunctival transition in the upper boundary of the defect Thus the upper fornix is almost obliterated in the coloboma area In relaxed sleep there is partial exposure of the cornea and sclera while exposure does not exist when forcefully crying



Fig 1a
The girl in normal sleep

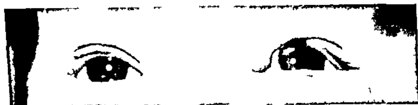


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ditary factors can not be found The mother of the child was not exposed to x rays and drugs or suffered from known infectious diseases during pregnancy Serum tests for lues and toxoplasmosis were negative in mother and child The delivery was uncomplicated and there were no nutritional problems in the postnatal period The chromosome examination showed a normal female pattern without trisomy or other abnormalities

The present case does not answer the pathogenetic questions about lid colobomes The harelip is a well known defective closure of a foetal cleft while the formation of the lids does not present cleftformation at any stage The lid folds appear about the 16 mm stage and gradually extend over the eyeball The upper and lower lid fuse in the 32 35 mm stage and separate again in the 6th 7th month The structures of the lid margin are differentiated during the period of adhesion and a defective adhesion has been suggested as responsible for the lack of normal development causing defective eyelids This concept however implies that the defects in our child have developed in different foetal stages since the harelip is already a fact when the fusion of the eyelids starts In older literature[4] [11] the outside mechanical pressure due to amniotic bands was strongly advocated These problems are discussed elsewhere (Mann[9] Duke Elder[3] and Waardenburg[12]) and will not be repeated here as our case does not render proof for any of the current theories

An other possibility is of course that the coincidence of the two pure defects in our child – instead of being part of a syndrome – is the extreme seldom statistical coincidence of two unrelated developmental mishaps The surgical care of Danish children born with harelip and cleft palate is centralized to Diakonissestiftelsen s Hospital in Copenhagen among 3 4000 of these children coloboma of the eyelid has not been seen[4] until our patient who had her harelip repaired in november 1968

Summary

A report is given on a child with the seldom combination of palpebral coloboma and harelip

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Fig 1c

Demonstration of the almost obliterated upper fornix corresponding to the palpebral coloboma of the left eye

Consanguinity between the parents did not exist In the mothers family congenital defects could not be reported In a previous marriage the father had a son with harelip but normal eyes

Teratogenetic factors during the pregnancy did not occur (exposition for x rays malnutrition infectious diseases or drugs)

Discussion

In 1919 Thylmann[11] reviewed the literature concerning lid colobomes Out of 120 available cases only 6 % were single thus a great number of associated defects could be reported Among these were 17 patients with harelip and three with cleft palate

In more recent literature only a few cases with both coloboma of the lid and harelip can be found[1 7 8 1] The striking feature of these is the great number of deformities in each patient and "first branchial arch syndrome has been proposed as a name indicating the site of the developmental defect In this connection Saraux & Besnainou[10] mention the cases with supernumerary chromosomes in the 13 15 group always running a fatal course in a few months because of cerebral and visceral malformations also harelip and cleft palate are seen together with ocular defects and among these uveal coloboma while lid defects are not reported in these trisomy cases

In contrast our patient appears healthy in any respect except for the lid colobome and the partial harelip A halfbrother has a harelip but otherwise here

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DYSTROPHIA MYOTONICA AND RETINAL DYSTROPHY

BY

ERIK GODTFREDSEN and SVEND FAURSCHOU JENSEN

Dystrophia myotonica is a rare heredo familial disease with dominant inheritance equally frequent in males and females (Thomasen) The myotonia is typical localized mainly in the upper half of the body head neck and arms Shaking hands with the patient can therefore give a hint of the diagnosis Cataract is a well known cardinal sign Its typical morphology allows the opthalmologist to be the first to make a diagnosis of dystrophia myotonica

Less known and only recently substantiated is the fact that the ophthalmological symptomatology is much more complex including a subnormal intraocular tension and retinal dystrophy Recent investigations based on fairly large series have contributed towards an increased ophthalmological interest further accentuated by modern studies on aetiology pathogenesis and physiopathology which open out new perspectives to a better understanding of this puzzling disease (Refsum Sjåstad)

Own Observation

Our interest in the subject was aroused when a man aged 4 was admitted to Bispebjerg Hospital in July 1967 to be under observation for coronary thrombosis which was not verified however He had for many years received a disablement annuity owing to characteristic dystrophia myotonica and was referred to the Eye Clinic because of visual complaints Here he proved to be an old acquaintance whose history had been published by one of us (E G)

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20 years before on account of the extraordinary and not previously described concurrence of dystrophia myotonica and retino pigmentary dystrophy

The patient s present admission gave a welcome occasion for following him up and reviewing the literature

When the patient had been examined by us 20 years previously at the age of 26 he had the typical myotonic appearance with fronto parietal baldness, ptosis of both upper lids and muscular dystrophy of the neck (sternocleido mastoid) and arms The muscular disorder had come on at the age of 10-1? years Thorough examinations during repeated stays in a neuro medical unit revealed typical electro myographic findings The patient belongs to a myo tonic family (described in Thomasen s M D thesis 1948) Seven of the ?? members of the family were found to suffer from dystrophia myotonica The patient is a dizygous twin His twin brother has cataract but not myotonia

Our patient has been night blind as long as he can remember and th objective tests for such disclosed massive hemeralopia After the age of 18-? his visual acuity gradually decreased to 6/12 and the latest test on the present examination gave R E V 6/36 and L E V 6/18 The visual fields (see previous publication 1947) showed concentric constriction with moderate pro gression since our previous examination Ophthalmoscopy showed approxi mately the same conditions as in 1947 namely ill defined slightly yellowish pale optic discs very thin retinal vessels especially narrow arteries and dif fuse retinal atrophy Inferiorly scattered blackish brown lumpy pigments were seen though not of a bone cell form Electrophysiological examinations carried out in 1967 showed the electroretinograms to be totally extinguished and on electromyography of the external and internal recti a characteristic myotonic after activity and occurence of polyphasis potentials were noticed

Slit lamp examination revealed a typical moderately pronounced punctate posterior cataract with some progression during the past 20 years The intra ocular tension was 14 mm (applanation tonometry)

Epicrisis A patient aged 47 when followed up 20 years after the first examination by us displayed moderate progression of both dystrophia myo tonica and the ocular signs cataract and retinal dystrophy established by electrophysiological examinations to be a tapeto retinal degeneration The intra ocular tension was slightly below normal

Discussion

When our case was published 20 years ago it seemed natural primarily to consider the combination of the two rare diseases as a mere coincidence How

ever bearing in mind that tapeto retinal dystrophy constitutes an element of various neuro psychiatric syndromes (Laurence Moon s syndrome Refsum s disease or heredopathia atactica polyneuritiformis amaurotic idiocy and others) the possibility of a causal relationship was suggested Publications from recent years have borne out this hypothesis

Reports on this subject during the past 20 years (for references see *Junge*) including two recently published fairly large papers on thoroughly examined series of cases from the U S A (*Burian & Burns* 1966 25 cases) and Holland (*Junge* 1966 57 cases) both with identical conclusions have shown that dystrophia myotonica may be associated with retinal dystrophy This may manifest itself as in our patient but more often as a central macular dystrophy with streaks and pigmentations and with thin vessels Such changes are seen in up to 25 per cent of the patients but functional retinal changes demonstrated by electroretinography or electro oculography are noticed in a surprisingly much greater number up to 80 per cent The dark vision examinations showed a similar high frequency of pathological findings A few of *Junge s* patients were subjected to opthalmo pathological examination (*Manschot*) which revealed a retino pigmentary dystrophy with proliferation The conclusion is drawn by both the American and the Dutch investigators that in cases of dystrophia myotonica retinal dystrophy is a *frequent complication* both morphologically and in particular functionally and an integral component of the clinical picture Genetically as mentioned previously by *Franceschetti et al* a gene with a pleiotropic action must be supposed to be responsible

Both Burian & Burns and Junge subjected the intra ocular tension as well as the aqueous humour dynamics to careful examination and confirmed the observations made first by *Granstrom* (1937) and later by *Brand* These latter showed that the intra ocular tension is very low presumably owing not only to a reduced production of aqueous humour but also to an increased facility of outflow

From the experience gained partly from the literature and partly from the present investigations it is evident that in cases of dystrophia myotonica we must reckon with not one but three ophthalmological cardinal signs namely cataract retinal dystrophy and a low intra ocular tension These signs together with the remaining clinical picture characterized among other things by a pluriglandular insufficiency in particular gonadal atrophy tempts us to suspect a common pathogenic factor situated in the diencephalon especially the floor of the third ventricle where so many of the servo regulations of the organism are located Very recently *Refsum et al* undertook investigations confirming this suspicion By performing repeated pneumo encephalographies on a series of myotonia patients they demonstrated a progressive atrophy of the hypothalamus with an increased diameter of the third ventricle *Refsum et al* concluded that dystrophia myotonica is due to a lesion of the dience

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Thomasen E Myotonia Thesis Universitetsforlaget Aarhus 1948

phalon presumably on a metabolic basis Unfortunately neuro pathological investigations are not yet available Refsum s metabolic hypothesis was recently borne out by *Sjastad* who stated in his M D thesis (1967) that in dystrophia myotonica we must reckon with a disorder of the histamine metabolism Continued studies on this question particularly on the excretion of n acetyl histamine must be awaited however before further conclusions can be drawn

In this connection it is worth noting that the disease described by *Refsum* in 1946 (heredopathia atactica polyneuritiformis) having retino pigmentary dystrophy as its cardinal sign has been recognized within the last few years as an inborn error of metabolism that is a cerebro retinal lipoidosis with a defect of the chlorophyl metabolism and accumulation of phytic acid We have known through several years that other retinal dystrophies are including among the metabolic cerebro retinal diseases *(Cogan* 1968)

Summary and Conclusion

The ophthalmological cardinal signs of dystrophia myotica are in addition to cataract a subnormal intra ocular tension and retinal dystrophy morphological and especially functional with pathological ERG and adaptation curve The authors own case followed up after 20 years and recent literature are recapitulated (*Burian* & *Burns* 1966 *Junge* 1966) The results of recent Norwegian studies (*Refsum et al* 1967 *Sjåstad* 1968) suggest that dystrophia myotonica is a metabolic disease localized centrally in the diencephalon

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REFRACTION IN THE NEWBORN

BY

ERNST GOLDSCHMIDT

While the frequency of ametropia in adults has been comparatively well established by means of extensive population studies, the distribution of refractive errors in the newborn is not nearly so well known, and the findings of older and more recent investigators have been inconclusive, particularly as regards the incidence of myopia. This is of substantial importance for clarifying the etiology of myopia, and there is therefore still a vital need for comprehensive studies of the refractive errors both in the foetus and the infant. The present paper is concerned only with the refraction in the newborn.

Earlier Investigations

Most of the studies on refraction in the newborn and infants were made during the last century. A summary of the results obtained is given in Table 1. The refraction was assessed by means of an ophthalmoscope. A few comments may be made on the various investigations in question.

Jaeger (1861) examined 100 infants nine to sixteen days after birth. None of the infants were treated with mydriatics prior to the examination. 17 were found to be hypermetropic, 5 emmetropic and 78 myopic.

Ely (1880) determined the refraction state in 100 eyes in infants, 80 per cent of whom were less than two weeks old and the remainder up to eight weeks old. All the eyes, including those of the examiner, were dropped with atropine. Approximately identical refraction was found in girls and boys. *Ely* examined

Table 1

Survey of previous investigations of the refraction of newborn

Author	atropine	number of infants	number of eyes	hypermetropic	emmetropic	myopic	average refraction in diopters
Jaeger (1861)	–	100		17	5	78	
Ely (1880)	+		100	72	17	11	
Horstmann (1880)	+	40		28	8	4	
Königstein (1881)	+		562	552	10	–	
Schleich (1884)	+		300	300	–	–	+ 4.4
Bjerrum (1884)	+	87		61	23	3	
Horstmann (1884)	+		100	88	10	2	+ 2.4
Ulrich (1884)	?	10		10?	–	–	
Germann (188[illegible])	+	110		110		–	+ 4.84
Herrnheiser (189[illegible])	+		19[illegible]0	1918	–	2	+ 2.3
Biegel (1893)		39		39	–	–	
de Vries (1901)	+	78		62	11	5	+ 2.4

a further 49 eyes after application of a very weak atropine solution. This time *Ely* did not atropinize his own eyes. This examination revealed 29 hypermetropic, 4 emmetropic and 16 myopic eyes, i.e. a considerably higher frequency of myopia. *Ely* stressed the great technical difficulties involved in the examination.

Horstmann (1880) examined 40 infants between the ages of 8 and 20 days. Four infants had myopia from 0.5 to 1.0 diopter (D). In 1884 he examined a further 100 infantile eyes, two of which were found to be *myopic*.

Königstein (1881) found no cases of myopia among 562 eyes examined; only 10 were found emmetropic, the remainder being hypermetropic, most of them at a rate of [illegible] to 3 D. Slightly [illegible] *per cent* of the mothers were myopic.

Schleich (1884) examined 300 eyes, all of which proved to be hypermetropic. No fluctuations were demonstrated during the first 14 days of life, and no correlation between the birth weight and the refractive state was found.

Bjerrum (1884) is the only Danish ophthalmologist to have studied refraction in the newborn. He examined 87 infants from 7 hours to 14 days old. The refraction was measured by adjusting the ophthalmoscope to give a distinct image of the vessels surrounding the papilla. Of the 61 hypermetropic infants 38 had +4.0 and 15 had +2.0. *Bjerrum* mentioned that hypermetropia was particularly pronounced in the youngest infants (less than five days old) and decreased in those slightly older.

Ulrich (1884) examined 102 newborn infants, all of whom were hypermetropic.

Germann (1885) examined 110 infants up to 80 days old and found all to be hypermetropic. Examination of 168 eyes during the first month of life showed an average refraction of +5.57 D, while 40 eyes examined in the second month of life averaged +3.30 D.

Herrnheiser (1892) found myopia in only one case out of a total of 1920 eyes examined.

Biegel (1898) found only hypermetropia in 39 babies, while in a study comprising 78 infants *de Vries* found five cases of myopia.

A few contemporary investigators used retinoscopy as a method of estimating the refraction.

Franceschetti (1935) assessed the refraction in 200 eyes in infants from 8 to 16 days of age. The retinoscopy was made in both the horizontal and the vertical meridians resulting in mean values of +1.4 D and +2.5 D respectively. The standard deviation in these observations fitted quite well the expected deviation in a normal distribution.

Table 2

Classification of types of refractive errors in 1000 eyes of infants
(Cook & Glasscock (1951))

	White	Negro	Total	%
Simple hyperopia	168	271	439	43.9
Hyperopia with astigmatism	126	165	291	29.1
Simple myopia	49	118	167	16.7
Myopia with astigmatism	15	49	64	6.4
Mixed astigmatism	7	22	29	2.9
Plano	3	5	8	0.8
Cataracts	2	0	2	0
Total	370	630	1000	100.0

Cook & Glasscock (1951) examined the eyes of 1000 newborn infants Prior to the examination atropine ointment was applied four times at intervals of six hours The investigation included 10 premature babies Some of the data are recorded in Table 2

Author s Investigations

The present study comprises 356 infants from 2 to 10 days old born in the Maternity Departments of *Rigshospitalet* Copenhagen All the infants had a birth weight in excess of 2500 grammes In order to obtain cycloplegia a 0 5 % atropine solution was given 24 hours prior to examination Where the cycloplegia was found to be insufficient the dose was repeated The refraction was determined with a retinoscope at a distance of 50 cm

Table 3
Refraction in 356 infants

Refraction in diopters		Boys	Girls	Total
Hypermetropia	8	1	–	1
	7	–	–	–
	6	–	–	–
	5	2	4	6
	4	13	7	[illegible]0
	3	[illegible]4	15	39
	2	27	30	57
	1	40	36	76
Emmetropia		3	34	71
Myopia	1	19	1[illegible]	36
	[illegible]	11	11	2[illegible]
	3	3	6	9
	4	4	5	9
	5	1	2	3
	6	4	1	5
	7	–	1	1
	8	–	–	–
	9	–	1	1
Total		1[illegible]6	1[illegible]0	356

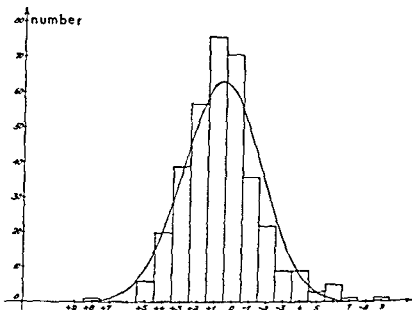


Fig 1
Curve of distribution of refractive states in 356 infants

Results

Table 3 gives the data the diopters being recorded in integral numbers The mean refraction in the boys was +0 76 D with a S D of 2 21 In the girls a mean of +0 47 D was calculated with a S D of 2 28 For the entire group the corresponding values are +0 62 D and 2 24 The standard error of the mean value is 0 1

The data suggest no difference in the refractive state in boys and girls.

A total of 86 myopic infants were found 42 boys and 44 girls The frequency of myopia in the entire material was 24 2 per cent

Figure 1 is a histogram of the data superposed on the normal distribution curve corresponding to the mean value and standard deviation A test of conformity between the observed and the normal distribution revealed that the present material deviates from a normal distribution (0 01 > P > 0 001) There are too few observations on the myopic side – apart from the highest degrees – in proportion to the quantity expected and there are too many in the sector from 0 to + 1

Comments

The various studies on refraction in the newborn have given widely varying results *Wibault* (1926) thinks that this must be due to the technical difficulties

involved in examining newborn infants However this can hardly be the only reason for the small incidence of emmetropia and myopia observed for instance by *Herrnheiser* In most of the older investigations in which an ophthalmoscope was employed we find an accumulation of certain degrees of ametropia and this might be due to the fact that most investigators made a systematic error possibly of a suggestive nature Retinoscopy probably gives more reliable results and a more exact indication of the refraction However this method also has its shortcomings since in many cases it is extremely difficult to assess the axial refraction on the restless eyes of a baby If the incidence of the beam is oblique the refracting power increases and a moving of the ocular refraction in the direction of myopia is obtained Furthermore retinoscopy often gives the impression that the posterior surface of the crystalline lens in many newborn infants is not uniform spherical a condition that may be due to structural refractive differences in the remnants of tunica vasculosa lentis and the primary vitreous This often simulates an astigmatism and shifts in refraction Myopia is seen more frequently when the refraction is determined by retinoscopy than by ophthalmoscopy but which method should be considered the most conclusive cannot be established The author s studies leave no doubt however that the eyes of many newborn infants are myopic

The drug employed to obtain cycloplegia may also be of significance It is a well known fact that the pupils of the newborn respond badly to mydriatics and in the present investigations preliminary attempts indicated that a substitution of the concentration of atropine from 0 1 per cent to 0 5 per cent was necessary in order to obtain definite cycloplegia and a reproducible refractive state

Besides the technique employed and the ability of the examiner some other conditions may influence the results It is well known that heredity is a determining factor in ametropia and it has also been established that the frequency of myopia varies within different population groups It thus seems likely that similar variations already are present in newborn infants In the present studies it is most plausible that the mothers do not constitute a representative group of fertile women since the Maternity Department in question partly receives unmarried mothers and partly women whose parturition is not expected to follow a normal course 34 mothers (9 5 per cent) had myopia and this is a frequency which is somewhat lower than the frequency found in Danish conscripts (Goldschmidt 1968) but much higher than in *Königstein* s investigations where only [illegible] per cent of the mothers had myopia Most of the previous works on the subject have also been carried out in hospital wards and it is possible that some of the divergences found in the various materials are due to variations in the genetic composition of the materials

Finally it must be emphasized that the developmental age of babies can vary considerably and that the birth weight is only one criterion of full term

birth In the last months of pregnancy and the first months of life the eyes develop considerably and there is reason to believe that the refraction also changes

Gleiss & Pau (1952) followed the refraction in premature babies and found that the degree of hypermetropia increased and myopia decreased during the last months of pregnancy (*The authors assume that the conditions of growth* were the same whether the babies were born or still *in utero*) At the first examination about one week after birth 12 of the 23 babies were found to be hypermetropic and 11 myopic Later 7 of the myopic babies became emmetropic or hypermetropic while only 4 remained myopic during the entire period of the investigation In three of these the degree of myopia decreased while in one, it increased None of the children had retrolental fibroplasia

Fletcher & Brandon (1955) examined 462 premature babies by ophthalmoscopy *136* having retrolental fibroplasia They observed *that* premature babies had fluctuating myopia that remained very pronounced even after application of various mydriatics Apparently accomodation played no significant part. *Premature babies weighing more than 1700 grammes had myopia up to* 6 D but it decreased during the first 4 to 10 weeks of life and at the age of six months the majority of their ocular fundi was seen sharply using ophthalmoscopic lenses from +1 to -3 D Furthermore the authors observed that the degree of myopia was higher when using an ophthalmoscope than in retinoscopy The most premature babies weighing less than 1250 grammes had immature eyes with a myopia from 10 to 20 D The degree of myopia decreased but it was not until the age of one year that it approached emmetropia The children with *retrolental fibroplasia also demonstrated myopia the degree* of myopia depending on the degree of fibroplasia The degree of myopia also decreased in these children and emmetropia was almost reached However at the age of 3 to 6 months a tend in the direction of myopia appeared again with values of between 10 and 20 D which persisted as long as the children were followed up (for at least two years)

Birge (1955) likewise describes a special type of myopia that occurs in conjunction with stages 1 2 and possible 3 of healed retrolental fibroplasia

Graham & Gray (1963) compared the refraction in 98 newborn infants with birth weights over 2500 grammes with the refraction in 150 premature babies weighing mostly between 1500 and 2000 grammes The study *revealed that children* with a lower birth weight more often were emmetropic or myopic The refraction varied between +6 5 and -9 D

Castren (1959) examined a group of premature children *at the age* of eight years and compared their refractions with those of a normal material No discrepancies could be demonstrated

Thus *it may be concluded that the lack of conformity* between the various series of examinations may be due partly to the technical difficulties involved

as well as the method of examination employed and partly to differences in the genetic composition of the materials and to varying degrees of maturity of the infants

Even though certain reservations should be taken when judging the results of the many investigations of the refraction in infants during the first weeks of life a great deal of valuable information has still been obtained It must be considered as established that all degrees of ametropia are already to be found in the newborn and that myopia is not so rare as previously assumed Furthermore the distribution of the different refractions (the refraction curve) in infants deviates from that in adults The leptocurtosis seen in adults is much less pronounced in infants where the standard deviation accordingly is greater A definite mean refraction of the newborn cannot be stated but it is on the hypermetropic side in all reports In the author s studies the mean value is +0 62 D This does not deviate greatly from +0 53 D the mean value for adults advanced by *Stromberg* (1936) but the standard deviation found is 2 24 against *Stromberg* s 1 14

The question remains of whether it is possible to predict the final refraction of a child on the basis of its refraction as a newborn infant or whether the ocular refraction at this stage has little predictive value Various studies have shown a decrease in the average degree of hypermetropia during the first years of life but these examinations have not been carried out on the same children and consequently do not answer the above question In the author s material one child was found to have a hypermetropia of 8 D This child had three sibs who also had pronounced hypermetropia On the other hand none of the children with high myopia had parents or sibs with the same ametropia It must be assumed that in the majority of cases the degree of congenital myopia will decrease and the myopia may even disappear altogether since more cases of high myopia were found among the infants than among schoolchildren and conscripts (*Goldschmidt* 1965) In order to elucidate this question comprehensive longitudinal studies are needed

Summary

A survey of previous studies on the refraction of newborn infants indicates that congenital myopia is very rarely seen. However in more recent studies and in the author s investigations a much higher frequency of myopia is found The possible reasons for these discrepancies are discussed and it is concluded that the lack of conformity may be due partly to the technical difficulties involved as well as the method of examination employed and partly to differences in the genetic composition of the materials and to varying degrees of maturity of the children The need of longitudinal studies is stressed

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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(Heads Professor H Ehlers M D and J Edmund M D)
and the Eye Department Frederiksberg Hospital
(Head E Gregersen M D) Copenhagen Denmark

THE POLYMORPHOUS EXO PATIENT

Analysis of 231 Successive Cases

BY

E GREGERSEN

In 1958 *Knapp* stated There is wide disagreement about nearly all aspects of the outward deviations of the visual axes The physiology of the divergence function and the various aetiological factors in divergent strabismus have not yet been finally elucidated It is not definitely known whether the divergence function indicates an active process i e a positive innervation of the lateral rectus muscles or whether the divergence is merely a result of reduced con vergence tonus without any active participation of the lateral rectus muscles

The view that divergence function is an active process has many adherents int al *Bruce* (1935) *Adler* (1953) *Breinin & Moldaver* (1955) and *Ogle & Dyer* (1965) There are also many spokesmen of the opposite view i e that the divergence function is due o a reduced convergence tonus and should accordingly be considered a passive mecha nism (e g *Scobee & Green* (1946) *Jampolsky* (1963) cf also the review by *Costen bader* (1950))

The ophthalmological literature also gives very varied data concerning re fraction sex ratio clinical grouping and age distribution at the onset of squint ing for the patients with exotropia

Lagleyze (1918) found myopia in 40 % of his patients with exotropia *Mayou* (1935) n about 18 % and *Cass* (1937) in only 10 %

Cas (1937) found a striking preponderance of females more than 70 % of her pa tients be ng females

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Cass (1937) found a striking preponderance of females more than 70 % of her patients being females

According to *Lee & O Brien* (1950) 60 % of patients with exotropia do not start

squinting until after the age of 6 years In *Costenbader's* (1950) material on the other hand more than half the patients with divergence excess had their divergent strabismus before the age of 1 year

Clinical grouping also varies widely from one material to the other From about the turn of the century there are materials in which 18 % and 45 % respectively of all cases of exotropia were intermittent (*Lagley c* (1913) and *Schweigger* (1894)) On the other hand *Schlossman & Boruchoff* (1955) found that 85 % of their exotropic patients belonged to the intermittent group

Thus, many conflicting views and statements have been published in respect to the pathophysiology and clinical picture of exotropia By submitting the present material the author intends to contribute a share to the highly faceted clinical appearances of exotropia

Material and clinical grouping

The material is unselected and consecutive comprising all patients with exophoria and exotropia recorded in the Squint Clinic, Rigshospitalet Blegdamsvej, and Frederiksberg Hospital during a period of 18 months (1 10 1966 - 1 4 1968 and 1 2 1967 - 1 8 1968 respectively) It comprises a total of 231 patients with exodeviation (197 from Rigshospitalet and 34 from Frederiksberg Hospital), 146 of whom were females and 85 males The average age is 19 8 years extremes 1 year and 70 years

The material falls into the two main groups (a) *primary* (or "*essential*") exodeviations and (b) *secondary* exodeviations (The latter group comprises exodeviation which is secondary to anisometropia and to other ocular diseases including also esotropia) Exodeviation due to ocular muscle palsy is not included in the present analysis

Primary exodeviations were sub divided into (1) *exophorias* (2) *intermittent exotropias* and (3) *permanent exotropias* Group 1 is characterized by the fusion being able to keep the eyes in the right position in spite of the muscular imbalance In group 2 the fusion can only keep the eyes in the right position inconstantly and in group 3 the position of the eyes is abnormal all the time

These three groups were again sub divided into exophoria/exotropia remota*) propinqua**) or aequalis***) i e exodeviation more marked for distance for near or approximately the same for near and distance

The clinical grouping is shown graphically in Fig 1 It is based upon purely clinical and descriptive factors implying nothing concerning aetiology or mutual relationship between the groups The term exotropia remota is preferred to divergence excess because divergence excess makes one think of an over

*) implying ad objecta remota
**) implying ad objecta propinqua
***) implying distantia omni aequalis

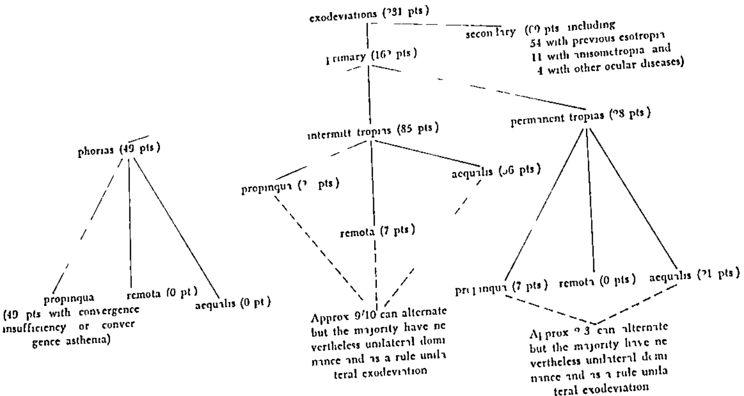


Fig 1
Types of deviation and distribution of patients

active divergence function which is not demonstrable by clinical analysis of the material The convergence insufficiencies are grouped under exophoria propinqua

The material as a whole group as well as the major subgroups were analysed for familial occurrence of strabismus time of onset refractive condition visual acuity squint angle binocularity and the co existence of other ocular or neurological diseases In addition the treatment and therapeutic results were recorded

Primary exophoria with symptoms (convergence insufficiency)

Among the primary exodeviations it seems most natural to start with exophoria or convergence insufficiency This group comprises 49 patients with convergence insufficiency or convergence asthenia practically all of whom were characterized by the existence of exophoria for near with symptoms (exophoria propinqua)

In all 49 patients the convergence insufficiency or convergence asthenia had started or manifested itself in the teens or later except in 3 cases where it was found in children aged 6 8 and 12 years The average age of patients with convergence insufficiency was 26 years (This group of patients with convergence insufficiency or exophoria propinqua includes only patients with primary convergence insufficiency)

Deviation and binocularity

All but 4 of the patients with convergence insufficiency had exophoria for near with symptoms, from 8 to 30 prism dioptres average about 20 prism dioptres*) The above mentioned four patients who had marked convergence insufficiency and low fusion reserves had exophoria of only 4 6 prism dioptres for near i e the exophoria itself was not greater than normal in these few cases

In some of the patients with convergence insufficiency intermittent exotropia for near may be provoked by repeated alternating cover tests On the other hand the patients with convergence insufficiency have no spontaneous intermittent exotropia for near except for the fact that they sometimes screw up one eye when reading Also the patients grouped as convergence insufficiency or as exophoria propinqua have orthophoria or exophoria (maximum 12 prism dioptres) but never exotropia for distance

In the majority of the 49 patients with convergence insufficiency or exophoria propinqua with symptoms the convergence near point was increased to an average of approx 20 cm (range approx 10 cm to more than 30 cm) How

*) The deviation was measured for near (30 cm) by prism bar and alternating cover test while the patient fixated a light

ever 13 of the 49 patients had a normal convergence near point at 5 7 cm The reason why they were nevertheless recorded as having convergence in sufficiency is that their convergence requires more effort than usual and is therefore more rapidly exhausted meaning that in such cases the condition may be called convergence asthenia or exophoria propinqua with symptoms

On the face of it it might seem that the greater the exophoria for near the remoter the convergence near point However the material shows no such relationship – All the patients with convergence insufficiency or exophoria propinqua have normal visual acuity in both eyes It may be mentioned also that 16 out of the 49 patients with convergence insufficiency have normal fusional reserves and normal stereopsis while the remainder have reduced fusional reserves and reduced stereopsis In the majority of cases there is uni lateral dominance most of the patients who screw up one eye when reading usually screw up the same eye when the convergence insufficiency manifests itself

Treatment

Orthoptic treatment was offered to all 49 patients with convergence insuf ficiency or exophoria propinqua with symptoms Nine did not want to start or complete this treatment because they felt that it was more of a strain than the disease itself Orthoptic treatment was supplemented in a couple of patients with minus lenses and in 3 patients over 50 years of age with prisms Three patients had operations for their convergence insufficiency as orthoptic treat ment alone was not enough

The therapeutic results are good in most of the 40 patients who completed the treatment 27 have been relieved of symptoms and are able to read without any complaint for several hours The treatment failed more or less in 13 patients mainly those whose general condition might be a little poor due to nervousness or overworking

The objective basis of the favourable therapeutic results in 27 out of the 40 patients manifested itself as normalization of the convergence near point and of the reduced fusional reserves The exophoria for near remained unchanged in 5 of the 27 successful cases while in the remainder it was reduced to about half the pre treatment values

Primary intermittent exotropia

The largest group among the primary exodeviations is made up by the inter mittent exotropias which counted 85 of the present patients i e just over one half of the total patients with primary exodeviation The average age among the patients with intermittent exotropia was 17 years 1 and 49 years being the extremes

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*) The deviation was measured for near (30 cm) by prism bar and alternating c er test while the patient fixated a light

in the bifoveal situation i e when the position of the eyes is normal is entirely normal in about one third of the patients while about two thirds have reduced fusion and stereopsis in the bifoveal situation

When the position of the eyes is normal correspondence is normal in all the patients During squinting many patients have marked suppression of the deviating eye Therefore it is not always possible to glean exact information about the correspondence in the squint situation However it was possible to demonstrate normal correspondence in the majority of the patients in the squint situation abnormal correspondence being demonstrable only in about one fifth of the patients in the squint situation This latter group of patients was distinguished in having now normal and now abnormal correspondence according to whether the eyes were in the normal position or squinting outwards (The following tests or examinations for correspondence were used Synoptophore after image Bagolini glasses and normal or paradoxical diplopia)

Treatment

Just over half the patients with intermittent exotropia were treated by operation and one quarter of this operated group also by orthoptics About one third had no treatment as they refused operation Orthoptic treatment was the only treatment given to about one seventh of the patients

Operation which in several cases was followed by orthoptics as already mentioned converted in just over two thirds of the operated cases the intermittent exotropia – amounting to an average of 30 35 prism dioptres – to exophoria averaging about 15 prism dioptres (only 5 patients having obtained orthophoria) These results which comprise two thirds of the operated cases must be called satisfactory an intermittent exotropia being converted into phoria which causes no symptoms in the majority of cases as the binocular function is normalized postoperatively spontaneously or with orthoptic training

The last one third of the operated cases comprises the poor therapeutic results the patients still having or again developing intermittent exotropia averaging about 20 prism dioptres This group comprises in particular cases in which the preoperative correspondence was abnormal in the squint situation

About one seventh of the patients had orthoptic training as the sole treatment In half of these cases the intermittent exotropia was converted into exophoria averaging about 20 prism dioptres while the other half failed to respond to the treatment

Primary permanent exotropia

The material includes 28 patients with primary permanent exotropia According to the data at hand the squint was congenital or had started before the age of one year in 12 of these patients while in 5 cases it had set in during early

In 49 of the 85 patients there are data as to when the squint set in In half of these patients the intermittent exotropia was congenital or had started before the age of one year while in about one quarter it had started at the age 1 12 years and in one quarter in the teens or later (oldest age at onset 46 years)

Types of deviation

About two thirds of the *patients with intermittent exotropia are of the aequalis* type, i e the deviation is approximately the same for near and distance About one quarter of the patients are of the propinqua type i e the deviation for near is greater than the deviation for distance (the difference having been arbitrarily fixed as 10 prism dioptres and over) Only about one twelfth of the patients have a deviation which may be called divergence excess or better exotropia remota In these patients the deviation for distance is greater than *for near (the difference having been arbitrarily fixed as 10 prism dioptres* and over) Vertical elements (unilateral hyperphoria tropia over functioning obliquus inferior and A or V syndrome) were mentioned in the records of 16 out of the 85 patients with intermittent exotropia

It should be emphasized that the common type of intermittent exotropia which occurs mainly when the patient is daydreaming or looking at remote objects must be designated in most cases despite its clinical appearance as an intermittent exotropia of the aequalis type This is because measurement of the basic imbalance or deviation in these patients i e the fusion free and accom *modation free exodeviation most often shows that it is approximately* the same for near and distance (The basic exodeviation was measured for near and distance by a prism bar and alternating cover test while the patient fixated a light the covered eye deviating outwards independently of accommodation and fusion)

The average squint angle in the exotropic situation is 30 35 prism dioptres 8 and 55 prism dioptres being the extreme limits Thus intermittent exotropia is *characterized in the great majority of cases by the eyes* being either in a normal position or squinting 15 20 ° Only 3 patients had squint angles of or below 10 prism dioptres and as already mentioned the smallest squint angle was 8 prism dioptres Thus so called microstrabismus" is rather uncommon among exo patients Only about one tenth of the cases were strictly unilateral while the remainder could alternate spontaneously or after a cover test *However* the majority of the alternators showed unilateral dominance

Binocularity

All the patients with intermittent exotropia have normal visual acuity in both eyes (In this connection it should be emphasized that this group is one of pri mary exodeviations patients with anisometropia and eye diseases other than exodeviation having been grouped as secondary *exodeviations) Binocularity*

tion for astigmatism of 0 5 dioptre or more either isolated or combined with a spherical refraction anomaly Patients with anisometropia of or over 2 dioptres are not included here since the exodeviations in these patients were classified as secondary exodeviations (The refraction was assessed on the basis of the refraction in the better eye i e the eve having better vision or when the vision was equal in both eyes the eye with less refraction anomaly It should be mentioned also that eyes with spherical and astigmatic refraction anomalies are listed as the spherical value + the 1/2 cyl while purely astigmatic eyes are listed as only the 1/2 cyl value)

Secondary exodeviation

The latter group of the exo patients comprises secondary exodeviations found in 69 patients i e almost one third of all patients with exodeviations

Exodeviation secondary to esotropia

Out of the 69 patients with secondary exodeviation 54 had previously had esotropia In 49 of these former esotropic patients the exotropia has *started after* a squint operation for esotropia (so called postoperative exotropia) while in 5 patients with previous esotropia the exotropia arose spontaneously i e un preceded by a squint operation (so called consecutive exotropia) The patients with exodeviation secondary to esotropia average 21 years in age 8 and 45 years being the extremes

Refraction visual acuity binocularity and types of deviation

The refraction in exotropic patients with previous esotropia differs from that in patients with primary exodeviation in a more common occurrence of hypermetropia > + 1 9 (53 % have refraction emmetropia to + 1 9 35 % > + 1 9 and 12 % myopia) 19 out of the 54 patients with previous esotropia have major or minor squint amblyopia Only 8 of the patients with exotropia secondary to esotropia have normal correspondence and in all 8 fusion is more or less reduced Two patients have alternating normal and abnormal correspondence and the remainder have abnormal correspondence

Exotropia secondary to esotropia is unilateral in just over one third of the patients (the amblyopic ones) and alternating in the remainder 46 out of the 54 patients with exotropia secondary to esotropia have permanent exotropia Thus intermittent exotropia is present in only 8 patients (the cases with normal correspondence) out of this group of secondary exodeviations

The average squint angle in the patients with exotropia secondary to esotropia is about 35 prism dioptres In two thirds the exodeviation is of the aequalis type Of the remaining one third all have exodeviation of the propinqua type except for one who is of the remota type

childhood and in the remainder the age at onset was unknown The average patient age is 17 years 3 and 51 being the extreme ages

Types of deviation visual acuity binocularity

The average squint angle in this group is 35 40 prism dioptres Three quarters of the patients have an equally large squint angle for near and distance (the aequalis type) while one quarter have a greater squint angle for near than for distance (the propinqua type) No patient with primary permanent exotropia is of the divergence excess or remota type Vertical elements (unilateral hyper phoria tropia and A or V syndrome) were recorded in only 4 cases

Only 3 of the patients with primary permanent exotropia have amblyopia (1/60 6/36, and 6/12 respectively) About two thirds of the patients with per manent exotropia can alternate spontaneously or after cover test while the remainder are unilateral

Only 4 out of the 28 patients with permanent exotropia have normal corres pondence and have preserved major or minor remnants of normal fusion The remainder exhibit abnormal retinal correspondence in all or in several of the various correspondence tests (in 6 of the patients the correspondence cannot be determined because of an early age or intellectual impairment)

Treatment

Seventeen out of the 28 patients had squint operations The operation was done on a functional indication in only 2 cases who had normal correspondence In the remainder it was done on cosmetic indication The 11 unoperated patients do not want an operation The results of the squint operations upon the 17 pa tients were as follows 2 obtained orthophoria 3 obtained exophoria of about 10 prism dioptres 3 developed esophoria of 5 10 prism dioptres and 9 have a residual exotropia averaging 10 15 prism dioptres

Heredity

The case records contain sufficient data concerning a positive or negative family history in only 72 out of the 162 patients with primary exodeviations Among these 72 patients 42 have a family history of strabismus while in the remaining 30 cases the family history was negative

Refraction

The refraction findings among the 162 patients with primary exodeviations do not seem to differ from normal Refraction was determined in 144 cases about 80 % of whom have a refraction of emmetropia to + 1 9 while about 7 % have hypermetropia exceeding 1 9 and about 13 % have myopia 12 % have correc

group is characterized by a reduced fusional ability due to impaired vision in one or both eyes

Exodeviation and neurological diseases

Neurological diseases which may entail or predispose to strabismus were present in 12 out of the 162 patients with primary exodeviations Six of these patients have cerebral palsy or other congenital encephalopathy 4 are more or less intellectually impaired and 2 have epilepsy In 10 of these 12 patients the squint is congenital while for the last 2 patients of this group the time of onset is unknown In 6 of these patients with neurological diseases the squint is permanent while in the other 6 it is intermittent – In this connection it may be mentioned that no patient of the material has a cranial deformity and that brachycephalus is mentioned in the records of only 4 patients

Summary

A clinical analysis of a successive material of 231 patients with exodeviations is submitted

The material falls into two main groups viz primary exodeviations and secondary exodeviations It is remarkable that the secondary exodeviations make up almost one third of the material and that approx every 4th exo patient had previously had esotropia which with a few exceptions had been treated by operation

In this material there is a female preponderance about 65 % of the patients being females both in the primary and in the secondary group presumably indicating merely that women are more likely than men to seek advice for squinting

The primary exodeviations were grouped as (1) exophorias with symptoms i e exophoria propinqua*) or convergence insufficiency (2) intermittent exotropias and (3) permanent exotropias Group 1 comprises about one third of the primary exodeviations group 2 about one half and group 3 about one sixth Thus intermittent exotropias were 3 times as common as permanent exotropias i e they make up 75 % of all the cases of exotropia The intermittent and permanent exotropias are sub divided into propinqua types*) remota types**) or aequalis types***) according to whether the deviation is greater for near for distance or approximately the same for near and distance

*) implying exophoria/ tropia ad objecta propinqua
**) implying exophoria/ tropia ad objecta *remota*
***) implying exophoria/ tropia distantia omni aequalis

Treatment

Of the 54 patients with previous esotropia 22 underwent operation for their exodeviation This improved the position of their eyes to an average of 10 15 prism dioptres of exophoria/exotropia Only one patient reverted to esotropia (8 prism dioptres) In the unoperated patients the cosmetic complaints due to the exodeviation are so moderate that they do not want operation Five out of the 8 patients with normal correspondence had orthoptic treatment for their intermittent postoperative exotropia In 4 patients this converted intermittent exotropia of a few degrees to exophoria of 2-10 prism dioptres

Exodeviation secondary to anisometropia

Eleven of the patients with secondary exodeviation have anisometropia averaging 5 5 dioptres (ranging from 2 8 dioptres) Only anisometropia of 2 dioptres and over is included, and patients with unilateral aphakia were excluded Six of the 11 patients have intermittent and 4 permanent exotropia averaging 15 20 prism dioptres while one patient merely has exophoria with symptoms The patients with intermittent exotropia have normal correspondence also in the squint situation whereas the patients with permanent exotropia have abnormal correspondence

According to the case records 8 out of the 11 patients with anisometropia have had the exodeviation right from birth, while the remainder had developed it in the course of childhood or youth In age these anisometropic patients with exodeviation average 23 years, 8 and 56 years being the extremes Four of the exotropic patients with anisometropia have amblyopia of 6/12 2/60 while the remaining patients have normal visual acuity in both eyes Conventional occlusion treatment of amblyopia was given without effect in one of these patients at the age of 8 years

Five out of the 11 anisometropic patients with exodeviation were treated by operation and 3 patients had orthoptic treatment One was offered a contact lens but never procured it As far as the therapeutic results are concerned it should be mentioned merely that in two operated cases the intermittent exotropia was converted into exophoria In the other 3 operated cases the therapeutic results were restricted to improving the cosmetic situation

Exodeviation and other ocular diseases

The last group of secondary exotropias comprises patients with eye diseases other than esotropia and anisometropia (Patients with bilateral aphakia were not included in the material) This group comprises only 4 patients all of whom have impaired vision in one or both eyes because of papillary atrophy (2 patients) albinism (1 patient) and macular degeneration (1 patient) This small

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HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

Aarhus D nmark

TRAUMATIC OPHTHALMIC ZOSTER

BY

ERIK HOLM PEDERSEN

It is known that zoster is caused by a virus (*Lipschut* 1921) but in all probability the condition is not provoked by an actual infection since its contagiosity is very slight or even doubtful It is more likely that the zoster virus is present in the organism and is activated by certain stimuli resulting in an attack of zoster (*Schonfeld* 1928 *Lehmann* and *Felkl* 1958)

In the literature great emphasis has been placed on the distinction between genuine (primary) and symptomatic (secondary) varieties (*Wohlwill* 1924 *Paton* 1926 *Walsh* 1947 *Thomas* 1955) Symptomatic zoster is believed to occur when certain definite causes can be demonstrated These causes may be either of a generalised or a local nature

Among generalised diseases which most commonly provoke zoster are lymphatic leukaemia and Hodgkin s disease but influenza may also act as a trigger mechanism Intoxication by chemical agents (including drugs given in therapeutic doses) is known to be an exciting factor Among these agents arsenicals have for a long time been known to serve as a trigger mechanism As early a 1868 *Hutchinson* described zoster in a patient treated with arsenicals and many other cases have since been added inter alia one in a 7 year old boy who was under treatment for chorea (*Pearce* 1930) To the list of toxic agents capable of exciting zoster *Baird* (1943) added lead bismuth mercury sulphathiazole and carbon monoxide

In many cases of zoster local processes around the involved sensitive ganglion have been demonstrated such as tuberculosis syphilis tumours osteomyelitis and fractures

The material was analysed for heredity time of onset patient age refraction amblyopia binocularity, treatment and therapeutic results

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Among generalised diseases which most commonly provoke zoster are lymphatic leukaemia and Hodgkin s disease but influenza may also act as a trigger mechanism Intoxication by chemical agents (including drugs given in therapeutic doses) is known to be an exciting factor Among these agents arsenicals have for a long time been known to serve as a trigger mechanism As early as 1868 *Hutchinson* described zoster in a patient treated with arsenicals and many other cases have since been added inter alia one in a year old boy who was under treatment for chorea (*Pearce* 1930) To the list of toxic agents capable of exciting zoster *Baird* (1943) added lead bismuth mercury sulphathiazole and carbon monoxide

In many cases of zoster local processes around the involved sensitive ganglion have been demonstrated such as tuberculosis syphilis tumours osteomyelitis and fractures

In the absence of such local stimuli the zoster is described as *primary*. Attempts have been made to reveal differences in the course of the disease in the two groups, e.g. with regard to the intensity of the pain and the scar formation, but no convincing differences have been demonstrated. It is clearly evident (1) that, as mentioned by *Wohlwill*, a subclinical local process may be involved in a "primary" zoster, and (2) that a local process may be unjustly incriminated as the provoking factor. In addition, since, as remarked by *O'Neill* (1945) and *Woods* (1956), both genuine and symptomatic zosters are caused by the same virus, it would seem reasonable to change the classification into one of cases with and without known exciting factors – a classification which would, however, be of little practical value and in which zoster does not differ from many other diseases, e.g. pneumonia and herpes simplex.

However, external stimuli have also been suspected of being capable of provoking zoster, and in this connexion attention has been focused on both somatic and emotional traumata.

In the voluminous literature on zoster, somatic trauma has in some cases been assumed to serve as a trigger mechanism. In 1928 *Schönfeld* reported three cases of ophthalmic zoster, associated with permanent impairment of vision, which were preceded by a local trauma. Compensation was granted to all three patients in spite of the fact that doubt was entertained as to a causal relationship between the trauma and the zoster. In 1935 *Ammann* collected six cases of traumatic ophthalmic zoster and one of maxillary zoster from the literature and added a case of ophthalmic zoster which he has personally observed. Five of these cases had been preceded by mechanical traumata to the orbital region, two by chemical traumata, and one by a burn on the face after an explosion.

Several authors have suggested that an emotional trauma may also be the exciting factor. This was mentioned by *Pick* in 1904, and *Schönfeld* cited three other authors (Haddon, Pochin, Roche) who had considered this possibility. *Hartz* (1935) observed zoster in a man who, a few days before, had been involved in a road accident without sustaining any injuries, and *Bjork* (1950) described a case in which the patient had been exposed to intense physical and mental stress for two weeks immediately before the eruption.

I have been unable to trace any statements as to the frequency of traumatic provocation of ophthalmic zoster, and it must, in fact, be admitted that it is difficult to provide a sufficiently large number of patients for a statistical evaluation. I have had the opportunity to study the problem in a series of 204 patients who represented the follow-up group of a total of 471 cases seen in Copenhagen hospitals over the 20-year period from 1932 to 1951.

Local trauma to the subsequently affected side of the face was stated to be the cause of the zoster in 13 cases. Mechanical traumata were most frequently suspected (nine cases). The traumata were those often sustained in everyday life: the patients had run against an open door or window, had had a fall

or been hit by a handball or a snowball A burn was believed to be the cause in one case and excessive exposure to sunlight in two Finally one trauma was due to a chemical agent viz slaked lime in the eye The periods elapsing be tween the trauma and the development of zoster varied from 12 hours to 9 days

An emotional trauma was suspected to be the provoking factor in 60 cases Of these 55 had been exposed to long continued mental strain such as endo genous depression financial worries illness and deaths in the family quarrels at the place of work or at home and over exertion A few patients stated spon taneously that they had felt that something was going to happen

The remaining five had been exposed to acute emotional traumata A brief description of these cases is given below

A man aged 65 was down in his cellar to fetch some fuel The light went out, but suddenly another light was turned on and he saw his own enlarged shadow on the white wall He became greatly shocked The next morning itching on one half of the forehead began followed a few hours later by the eruption of zoster

A woman aged 65 was told at 2 o clock in the morning that the factory in which she worked and to which she felt greatly attached had been blown up A few hours later pain in the face began, and exanthem appeared two days later

A man, aged 61 received a letter in the morning saying that his son had a debt of 500 kroner The zoster erupted the same evening Incidentally it afterwards appeared that the letter was addressed to another person

On returning home at 4 o clock in the afternoon, a woman aged 65 found that a thief had broken into her flat. The eruption developed during the following night (It should be added that the woman was at that time under treatment for syphilis with neosalvarsan and bismuth)

A woman, aged 40 witnessed that a neighbouring house was blown up The erup tion appeared two days later

A control group was desirable in the evaluation of the relevance of the above mentioned potential causes I therefore asked 204 patients who applied for ophthalmic examination if they had within the last few months been ex posed to somatic or emotional traumata similar to those being suspected of giving rise to zoster The patients in the control group were selected so that the age and sex distribution was the same as among the zoster patients

Sixteen of those questioned stated that they had been exposed to such trau mata Three had sustained head injuries one had had a fall with a motorcycle 20 days before two had experienced traumata to the forehead 2 and 14 days before Eight had for some time been exposed to emotional stress which had lately been accentuated Of these three had financial worries two had severe somatic and three had mental illnesses in their families In five the stress had occurred within the last three weeks in one case the father had died in an other a touchy mother in law had moved into the home A young man had recently been told that his fiancée had become pregnant and another had

learnt three weeks previously that he possibly suffered from renal tuberculosis Finally one patient had recently failed in an examination

Two possibilities must be considered in determining whether the control group is representative (1) If some of the individuals applying for ophthalmic examination came because of somatic or emotional trauma the figures would be too high (2) If some stayed away for the same reason the figures would be too low From the (brief) interviews I had with the patients I gained the impression that none of the 16 patients with a history of recent trauma came because of that It is of course possible that a few patients with a history of trauma may have postponed the ophthalmic examination but this scarcely occurred in so many cases that it can explain the great difference in the figures in the two groups

On the other hand, as far as acute emotional traumata are concerned the control group is scarcely representative since it is likely that such patients would postpone their visit to the eye specialist for a few days However the relation between the experiences of the patients and the eruption of zoster in the five cases reported above is so much alike that it is difficult to reject that a causative factor is involved

Thus, the distribution of traumata in the two groups was as follows

	Series of patients	Control group
Somatic trauma	13	3
Chronic emotional trauma	55	13
Acute emotional trauma	5	0

Statistical analysis of the two groups by means of the chi square test (Dr Aage J Therkelsen) revealed a significantly higher frequency of somatic and emotional traumata among the patients than in the control group viz $0.02 < P < 0.05$ and $P < 0.001$ respectively

Conclusion

The study revealed evidence in support of the assumption that a local somatic as well as a chronic or acute emotional trauma may be the exciting factor in ophthalmic zoster

Summary

Zoster is caused by a virus and may be provoked by morbid processes involving the sensitive ganglion

In a series of 204 patients with ophthalmic zoster and a control group of the same size it was studied if external traumata are capable of provoking zoster

In 13 cases the patients stated that the zoster had been provoked by a local somatic trauma whereas such a trauma had been sustained in only three cases in the control group The corresponding figures for long continued emotional traumata were 55 and 13 Finally five of the zoster patients expressed the view that an acute trauma was the exciting factor

The chi square test revealed a statistically significant difference between the two groups The results of the study thus suggest that a local somatic as well as a chronic or acute emotional trauma may provoke ophthalmic zoster

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Zoster is caused by a virus and may be provoked by morbid processes involving the sensitive ganglion

Diagnostic Excision and Puncture

There exist several methods of taking biopsy specimens suitable for settling the nature of a suspected intraocular tumour Thus in some cases tumour cells can be demonstrated in humor aspirated from the aqueous chamber in other cases a definite answer may be obtained from a specimen of suspected tumour tissue removed by excision or puncture However the latter procedures are often avoided (*Jensen* and *Ry Andersen* *Makley Sanders* etc) since a negative finding by no means rules out the presence of a tumour and since the procedures themselves inherently imply a small risk for the spreading of tumour cells resulting in implantation metastasis (*Jensen* and *Ry Andersen*) It is therefore usually recommended that the diagnosis of a tumour should be based on the clinical picture particularly on positive observations with trans illumination in serous retinal detachment (*Makley*) Even in some of these cases one cannot avoid enucleating an eye with other diseases than tumours e g a massive choroidal haemorrhage or degenerative lesions of a proliferative type Personally I have considered it my duty in cases with suspected intra ocular tumours unsuitable for surgery or irradiation to take a biopsy for immediate histological examination of frozen sections The operated eye was meanwhile provisionally closed so that enucleation could be done at once if the pathologist reported a malignant process In a few instances I have tried to take puncture specimens but I feel that the procedure is not only unreliable but also that the risk for a tumour spread along the puncture canal is possible Cases suitable for excision of a biopsy specimen are mainly those with a tumour in the anterior part of the uvea inappropriately situated for radical surgery The majority of the tumours in the most posterior parts of the eye are usually not accessible This procedure was adopted in a limited series of cases in the period from 1961 to 1963 and only 4 of them operated on at the Eye Clinic of Umeå have been followed long enough for a proper evaluation These will be described briefly in the following

Case 1 V A male age 42 years Shimmering before the right eye since half a year At examination the left eye was found normal with V A = 1 0 The right eye had V A = 0 4–0 5 In the fundus about 3 or 4 disk diameters below the disk a tumour protruded about 13 diopters and at this site a shadow was found with trans illumination After temporary resection of the inferior rectus muscle and electric cauterization of the scleral surface overlying the tumour a piece was excised from the tumour after an incision of the sclera *Histological* examination revealed a *malignant* melanoma Since no metastasis had been found the eye was enucleated At examination 6 years later the patient was healthy and had no pathological changes in the prosthetic cav ty

Case B H female age 51 years After noticing shimmering and entopsies before the right eye for 10 years the patient consulted an oculist who immediately referred her to the hospital with a suspicion of a *malignant* melanoma. The visual acuity of

HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the Department of Ophthalmology University of Göteborg
(Head Professor A Huggert M D)

EXPERIENCES ABOUT SOME MEANS OF AVOIDING ENUCLEATION FOR SUSPECTED INTRAOCULAR TUMOURS

BY

ARNE HUGGERT

Enucleation has long been the therapy of choice in suspected or diagnosed intraocular tumours of varying origin (retinoblastoma malignant tumours from various uveal parts metastasis to the eye) When one has experience of eyes enucleated solely for a suspected intraocular tumour (e g in proliferative macular degeneration and in benign uveal melanoma or in inflammatory proliferative processes in the eye) knowing that some kinds of tumour respond very well to irradiation or radical surgery then one becomes increasingly critical towards enucleation as the treatment of choice in suspected intraocular tumour Hence there is every reason in the individual case to make the diagnosis as certain as possible and in all suitable cases to use radical surgery or irradiation or other therapy in preference to enucleation On the basis of experiences from this clinic the present investigation is designed to show

1 How in doubtful cases one can obtain a *definite* pathoanatomical diagnosis before enucleation becomes unavoidable and

2 How in certain tumour types one can find other radical therapy than enucleation

There exist several methods of taking biopsy specimens suitable for settling the nature of a suspected intraocular tumour Thus in some cases tumour cells can be demonstrated in humor aspirated from the aqueous chamber in other cases a definite answer may be obtained from a specimen of suspected tumour tissue removed bv excision or puncture However the latter procedures are often avoided (*Jensen* and *Ry Andersen* *Makley* *Sanders* etc) since a nega tive finding by no means rules out the presence of a tumour and since the procedures themselves inherently imply a small risk for the spreading of tumour cells resulting in implantation metastasis (*Jensen* and *Ry Andersen*) It is therefore usually recommended that the diagnosis of a tumour should be based on the clinical picture particularly on positive observations with trans illumination in serous retinal detachment (*Makley*) Even in some of these cases one cannot avoid enucleating an eye with other diseases than tumours e g a massive choroidal haemorrhage or degenerative lesions of a proliferative type Personallv I have considered it my duty in cases with suspected intra ocular tumours unsuitable for surgery or irradiation to take a biopsy for immediate histological examination of frozen sections The operated eve was meanwhile provisionally closed so that enucleation could be done at once if the pathologist reported a malignant process In a few instances I have tried to take puncture specimens but I feel that the procedure is not only unreliable but also that the risk for a tumour spread along the puncture canal is possible Cases suitable for excision of a biopsy specimen are mainly those with a tumour in the anterior part of the uvea inappropriately situated for radical surgery The majority of the tumours in the most posterior parts of the eye are usually not accessible This procedure was adopted in a limited series of cases in the period from 1961 to 1963 and only 4 of them operated on at the Eye Clinic of Umeå have been followed long enough for a proper evaluation These will be described briefly in the following

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Case 2 B H female age [illegible] years After noticing shimmering and entopsies before the right eye for 10 years the patient consulted an *oculist* who immediately referred her to tl e hospital with a suspicion of a malignant *melanoma* The visual acuity of

the eye was 0 9–1 0 In the lower part of the fundus a dark mass protruding about 15 diopters extended from 3 5 disk diameters below the disk all the way to ora serrata *With transillumination* a faint shadow was seen in the anterior part of the bulb peripheral to the protrusion The shadow was so faint that there were no solid grounds for suspecting melanosarcoma Consequently a proper diagnosis could not be arrived at without a pathological examination Signs of metastasis could not be found A piece excised in the same manner as in Case 1 revealed on examination of frozen sections a malignant melanoma and the eye was immediately enucleated Pathological diagnosis disclosed melanosarcoma Primary healing was uneventful When examined 5 years later the patient was in good health without any sign of metastasis either generally or locally in the orbit

Case 3 V B male age 48 years After 3 weeks of slight irritation in one eye the patient was found to have V A = 0 9 Half a disk diameter below the optic disk the fundus exhibited a dark region protruding 1 diopter Transillumination disclosed a distinct shadow No metastasis was found No specimen could be excised from the tumour due to its location close to the disk *With transillumination and simultaneous ophthalmoscopy* a puncture specimen was obtained Pathological examination disclosed some cells with a dark chromatin pattern but no definite melanosarcoma Enucleation was therefore postponed Since tumour had increased in size 3 months later and caused a local retinal detachment the eye was enucleated Pathological examination at this time disclosed localized melanosarcoma No melanoma cells were found along the puncture canal Neither general nor local metastases have been demonstrated during 6 years of follow up examinations

Case 4 L L female age 30 years For 6 months the patient had experienced flashes and flames before the lower temporal quadrant of the left eye V A = 1 0 A mass was found that protruded 10–11 diopters and was situated at the lower nasal part of the fundus At this site a distinct shadow was noticed on transillumination Since enucleation was refused by the patient initially a sample was taken after cauterization at the site of the shadow When a melanosarcoma had been demonstrated in frozen sections the patient submitted to enucleation The eye contained a malignant melanoma in the equatorial plane Signs of metastases have not been found at an examination 5½ years later and the patient was in good health at this occasion

Surgical Treatment of Intraocular Uveal Tumours

It has long been known that malignant tumours of the iris give symptoms late grow very slowly and present metastasis late Accordingly such tumours readily lend themselves to surgical treatment particularly since the whole tumour usually can be radically removed by local iridectomy In recent years it has been shown by Stallard Muller Linnie and Winter that a successful removal can be carried out also of tumours in the chamber angle in the ciliary body

or at the anterior part of the choroid In such cases iridectomy is combined with partial cyclectomy or local choroidectomy Iridectomy alone is a fairly common procedure in cases of malignant or suspected malignant tumours of the iris and I shall therefore limit my discussion to my cases of iridocyclectomy or choroidectomy The surgical procedure in such cases was presented in this journal by *Palm* and *Linder* 1968 My own series comprises merely 6 cases which will be described below

Case 1 K E male age 52 years The patient had had a brown spot on the right iris for at least 20 years when examined at age 50 by a Medical Officer who sent him to an oculist. The latter found a naevus occupying the chamber angle between 3 and 4.30 o clock which adhered to the posterior surface of the cornea Two years later the tumour had increased in size and enucleation was proposed The rim of the pupil was now turned inward V A was 1 0 and no metastasis could be detected An excision was performed which included the base of the iris and the adjacent part of th ciliary body The procedure could be carried out with only a minor loss of vitreous humor Histological examination of the specimen revealed that the tumour was radically removed and probably consisted of a malignant melanoma Postoperatively V A was 1 0 with astigmatic correction and vision remained at this level , years later Neither metastasis nor local tumour growth was found at this instance

Case 2 S E male age 40 years Myopic V A = 1 0 with correction The patient had noticed that the right pupil had been oval shaped for the past 6 *months* An oculist found a greyish tumour mass protruding forwards from the iris at 5 o clock and occluding the chamber angle Transillumination disclosed a shadow *which was* not connected to the normal shadow of the ciliary body Since no metastasis was found iridectomy with partial cyclectomy was performed *Pathological diagnosis* of the specimen revealed a hyperpigmentation of the iris The presence of naevi or signs of malignancy could not be demonstrated Two months *postoperatively* V A was 1 0 with astigmatic correction but vision has later decreased because of cataract

Case 3 G E male age 68 years A unilateral tumour of the iris was observed at a routine eye examination on account of hypertension V A = 1 0 with correction +1 75 The tumour was dark pigmented and protruded so that it occupied the chamber angle between 9 and 10 30 o clock Transillumination showed a shadow *of a type seen in cys s* which was separated from the shadow of the ciliary body Since the tumour had exerted some pressure on the lens the latter showed a cataract *in adjacent parts* The *lesion* was interpreted as a cyst at the base of the iris and surgery was postponed Howe er 3 months later a distinct growth had occurred *and the lens had become* mo e cl udy so an excision was done A pea sized practically solid *mass* was *found* at the b undary between the ridic base and the ciliary body Pathological examination disclosed massive naevus formation of *uncertain* malignancy but apparently with expansive growth The cataract has gradually progressed during the subsequent course

Case 4 G J male age 57 years The left eye had been *enucleated* 45 years before after a perforating wound For some time the patient had noticed a shadow in the right part of the visual field *of the remaining eye Extensive* retinal detachment was present and transillumination revealed a dense shadow 7 × 10 mm in size Since the corrected V A was 0 4 and s gns of *metastasis* were not *detected* a *local* radioactive

the eye was 0 9–1 0 In the lower part of the fundus a dark mass protruding about 15 diopters extended from 3 5 disk diameters below the disk all the way to ora serrata With transillumination a faint shadow was seen in the anterior part of the bulb peripheral to the protrusion The shadow was so faint that there were no solid grounds for suspecting melanosarcoma Consequently a proper diagnosis could not be arrived at without a pathological examination Signs of metastasis could not be found A piece excised in the same manner as in Case 1 revealed on examination of frozen sections a malignant melanoma and the eye was immediately enucleated Pathological diagnosis disclosed melanosarcoma Primary healing was uneventful When examined 5 years later the patient was in good health without any sign of metastasis either generally or locally in the orbit

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treatment with a cobalt applicator was carried out Half a year later V A had declined to 0 2 The defect in the visual field and the retinal detachment had both increased Surgery was decided although the main part of the tumour was localized behind the ciliary body towards the equatorial region of the eye The operation was performed by making one incision along the corneal limbus and 3 additional ones extending radially backwards from the limbal one so that two large flaps could be folded up With this procedure the tumour could not be excised entirely since it extended too far backwards The postoperative V A was 2/50 The visual field remained fairly unchanged but the retina was reattached At a follow up examination one year postoperatively the patient s condition was unchanged and no signs of metastasis were found despite the fact that the pathological examination had shown the presence of a malignant melanoma Histologically the activity of the melanoma persisted in spite of the preceding irradiation Four months later the condition still remained unchanged but then the patient suddenly fell ill with cerebral frontal lobe symptoms and one month later died of a cerebral metastasis His visual acuity remained unchanged up to the very last month

Case 5 M E male age 41 years A tumour of the iris in one eye was known for 8 years At examination it had shown tendencies to grow The corrected V A was 0 9–1 0 and a greyish brown tumour was seen protruding and occupying the chamber angle between 4 and 5 o clock By a local iridocyclectomy the tumour could be separated from the surrounding normal iris and ciliary body Minor amounts of vitreous humor were lost Pathological examination revealed a malignant melanoma which had been radically removed A year later V A was still 1 0 and the lens clear

Case 6 C A male age 25 years The patient who was of Arabian origin had been cross eyed as a child and was hyperopic with anisometropia and amblyopia in one eye (V A = 0 3) A tumour of the iris was accidentally discovered in the better eye which had a V A of 0 9 No metastasis could be found The tumour occupied the chamber angle between 9 30 and 11 30 o clock and transillumination revealed a shadow superimposed on that of the ciliary body Local iridectomy was performed between 9 and 11 30 o clock A pea sized tumour was found posterior to the iris extending towards the chamber angle and into the ciliary body parts of which were also resected The posterior part of the tumour could be readily distinguished from the surrounding normal tissue Pathological examination revealed a melanosarcoma *Upon discharge 18 days postoperatively* V A was 0 5–0 6 *and* the wound well healed At a follow up examination 18 months postoperatively V A was 0 7 with +4 correction and there were no signs of metastasis or local recurrence

Irradiation of Intraocular Tumours

As appears from one of the preceding cases one must choose surgery in cases of malignant melanoma that do not respond to local irradiation The reverse is usually the case *however and irradiation* is used when the surgical procedure has not been effective In the series of patients reported below irradiation

was on the whole limited to the following 3 groups 1) malignant melanoma unsuitable for surgical therapy 2) retinoblastoma and 3) metastasis to the eye from primary tumours elsewhere in the body

Radiation Treatment of Malignant Melanoma of the Uvea

Irradiation was only used occasionally for treating malignant melanomas since these tumours usually have a limited sensivity to such therapy The cases thus treated are described in the following case reports

Case 1 W B age 41 years Retinal detachment was observed in one eye and was due to a tumour with a size of 2 optic disk diameters and protruding 7 diopters It was located immediately behind the equator and was treated with radioactive cobalt in a dosage of 90 000 r at a depth of 1 mm and 7000 r at a depth of 3 mm for 40 hours When last examined 3½ years after the treatment the patient s V A was still 1 0 and locally on the fundus there was an atrophic area measuring two optic d sk diameters and protruding 1-2 diopters

Case L M age 54 years A pigmented focus similar to that of a tumour was discovered in one eye Its size was 4 disk diameters and it protruded slightly and was located in the equatorial region V A was 1 0 and neither metastasis nor any primary tumour elsewhere in the body could be demonstrated Three years later the size of the tumour had increased slightly and it was treated with a cobalt application of 15 000 r at a depth of 1 mm and 3000 r at 3 mm for 30 hours Four years after the treatment the local picture was on the whole unchanged and metastasis was not found suggesting that the p gmented lesion was a benign one

Case 3 A C age 47 years At a routine eye examination a tumour was discovered ab out optic disk diameters from the central fovea with a diameter of 2-3 disk diameters and a protrusion of 3 diopters Cobalt application with 12 000 r for 40 hours At the last examination 3½ years after irradiation V A had diminished from 1 0 to 0 -0 8 but the tumour had vanished and only a retinal atrophy was found at its site

Ca e 4 J K age 51 years Had noticed diminishing visual acuity on one eye A l cal detachment of the retina was discovered which on transillumination revealed a 10 by 10 mm shadow located 10 mm from the limbus Signs of metastasis were not observed In February 1960 a cobalt applicator was used giving 15 000 r over 30 h u s The condition was unchanged half a year later but in May 1963 the visual a uity had decreased and the tumour had increased in size It was then decided to en cleate the eye an l a large melanosarcoma with some necrotic and regressive hanges was found The greater port on of the tumour showed signs of cellular pr gression

Ca e 5 J A age 55 years During childhood a bullet had injured one eye which wa blind In September 1966 the patient consulted an oculist after having seen a

shadow before the other eye V A was then 0 5 with correction The lens was somewhat cloudy and in the fundus a large tumour was found which gave a dense shadow when transilluminated The tumour seemed to arise from the ciliary body and extended from 1 30 to 5 30 o clock It reached so far back that its posterior margin could not be distinguished Since surgery seemed useless x ray radiation was used in a dosage of 6000 r divided in 15 treatments This caused the tumour to diminish in size and the field of vision increased somewhat but an irradiation cataract appeared which in 1½ years became so dense that the lens had to be extracted

Radiation Treatment of Retinoblastoma

Although the effectiveness of radiation treatment is rather doubtful in uveal melanosarcoma such treatment can be very useful in retinoblastomas or tumour metastasis to the eye which usually are more sensitive for radiation Our experiences of radiation therepy in retinoblastoma have been reported elsewhere (*Rosengren* and *Tengroth* 1963 *Tengroth* and *Rosengren* 1968) Their reports may be consulted for further information on the nature of the cases and the results of the therapy Since publication of this last report 4 additional cases have been treated bringing the total number up to 14 cases One of the these four cases had a tumour that was so large that the cobalt applicator could not be used and therefore radiation treatment had to be given to the whole eye These doses did not have the desired effect and the eye had to be enucleated The remaining 3 patients had smaller tumours in the last eye the first eye was enucleated elsewhere The follow up period in these 3 cases is still very short but the tumours are definitely receding Clinical data on these patients will be given below

Case 11)* J C girl age 1 year No known tumours in the family The weight at birth was 2950 g and the girl had two older healthy sisters In 1967 a retinoblastoma was found in the right eye which was enucleated and the diagnosis was verified histologically The left eye then seemed normal However two weeks later a retinoblastoma focus was discovered in the left eye near the periphery of the fundus at 8 30 o clock and 2–3 disk diameters in size A cobalt applicator was applied for 40 hours Subsequent follow up examinations have revealed that the focus is receding satisfactorily

Case 12 A I girl age 1 year No relevant family history At 3 months of age the tension in the right eye was elevated and the cornea cloudy Three months later an intraocular tumour was suspected and the eye was enucleated It was found to contain a retinoblastoma Two weeks later large tumour masses were seen in the left eye covering more than 3/4 of the fundus including the optic disk and the

*) Case 11 of all the retinoblastoma cases seen at this clinic

macular region As the tumour was too large for cobalt radiation an attempt was made with high energetic electrons (Betatron therapy) This had no effect and that eye too had to be enucleated

Case 13 N P boy age 1½ years The father has a squint and the patient has had a strabismus since birth The pupil of the squinting eye was grey and the entire retina detached After enucleation a retinoblastoma was demonstrated and thereupon a large tumour occupying a quadrant of the fundus was found in the other eye as well A cobalt ball was applied in two separate positions for altogether 94 hours A month later a new focus about 2 optic disks in diameter was observed in the same eye Also this was exposed to ^{60}Co irradiation on two occasions Six months after the last treatment both foci were receding satisfactorily

Case 14 P J boy and 22 months old Both father and grandfather had retinoblastomas and had had one eye enucleated and the other eye healthy In March 1967 a retinoblastoma was discovered in the boy s left eye which was enucleated in another hospital A month later a tumour measuring 2 optic disk diameters was found in the boy s other eye Cobalt radiation was administered in May 1968 whereupon distinct regression has taken place

The results of radiation treatment in our 14 cases confirm the reports by others that small and solitary retinoblastoma foci respond very well to local radiation In cases with large tumours however this treatment is not satisfactory

Radiation Treatment of Metastasis to the Eye

Radiation treatment of tumour metastasis to the eye is less often chosen with the object of eradicating the tumour itself than in order to avoid untoward side effects in the eye from the tumour In recent years 2 cases have been treated for this reason one because the tumour was located in the iris and gave rise to an elevation of intraocular tension and the other because metastases to the choroid greatly reduced the patient s visual acuity The following information about these patients may be of interest

Case 1 S N age [illegible] Was operated on for cancer of the left breast in 1961 During the first 4 years after the operation there were no signs of metastasis In November [illegible] a metastasis to the choroid of the left eye was found and the eye enucleated A similar metastasis to the choroid of the right eye was discovered in 1966 and in March an additional metastatic tumour was found in the chamber angle of that eye resulting in reduced vision and elevated intraocular pressure The latter metastasis was treated locally with a cobalt applicator and the eye distress disappeared At her death a year later the eye had remained free from symptoms since the treatment

Case 2 C C age 66 was operated on for cancer of the right breast in 1963 Reduced visual acuity due to retinal detachment in 1966 Conventional therapy was ineffective and all signs pointed to the presence of a metastasis to the choroid Since the patient refused enucleation local irradiation therapy was instituted and this markedly improved her vision Metastatic tumours later appeared in the choroid of the other eye These tumours were also irradiated with temporary satisfaction

Summary

The author describes his own experiences of attempts to reduce the number of enucleations of suspected intraocular tumours partly by pointing out the possibility of making a more reliable diagnosis by biopsy specimens partly by the increased use of local surgery and local radiation treatment in cases where the diagnosis had been confirmed pathologically

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MUCOSUBSTANCES OF THE ACINI OF THE HUMAN LACRIMAL GLAND (ORBITAL PART)

I Histochemical identification

BY

O A. JENSEN I FALBE HANSEN
TOVE JACOBSEN and ANNETTE MICHELSEN

Histochemical investigation of the mucosubstances (MS) of the human orbital lacrimal gland has only been made in a few instances and mainly using the PAS reaction[1 2]

We have applied a number of histochemical methods to this part of the human gland supplemented by a biochemical analysis The latter will be published separately

Material and Methods

The orbital part of the human lacrimal gland was removed 17–18 hours after death in ten cases and pieces of the gland were removed in connection with enucleation of the eyeball in three cases The patients were half men half women 20–50 years old and had had no lacrimal disease.

The tissue was freed from fat and connective tissue cut into 1 mm thin slices and

This investigation was supported by a grant from Landsforeningen til Kræftens Bekæmpelse

immediately fixed in 4 % buffered neutral formaldehyde for 24 hours Lillie s ethanol formalin acetic acid[3] for 24 hours both at 4° C as well as 4 % formalin containing 0 5 per cent cetylpyridinium chloride (CPC)[4] at room temperature for 24 hours

In another two cases frozen sections of tissue removed during operation were stained directly

Routine paraffin technic was employed in the other instances From each gland about 65 sections were made

Deparaffinized hydrated sections were stained in the following ways (table 1)

1) The periodic acid Schiff reaction (PAS)[5 6]
2) PAS following diastase[a)] hydrolysis at 37° C for 60 min[5]
3) 0 5 per cent aqueous toluidine blue O[b)] for 20 min at pH 0 9 1 42 1 99 3 4 and 5 0 (TBL)
4) 0 1 per cent TBL in 30 per cent ethanol[7] at the same pH ranges
5) 0 1 per cent azure A for 10 min at the same pH ranges as for TBL (AA)
6) TBL and AA after oxidative deamination with ninhydrin for 30 min at 37° C[8]
7) Methylene blue extinction[9]
8) Alcian blue 8 GS (AB)[10]
9) 0 5 per cent AB 8 GX in 3 per cent acetic acid[11]
10) Colloidal iron stain (Hale s reaction) (CI)[11]
11) AB and CI both in combination with the Feulgen Rossenbeck reaction for DNA (AB F CI F)[1]
12) AB 8 GX PAS[11]
13) CI PAS[11]
14) Aldehyde fuchsin AB (AF AB)[13]
15) AB Safranin O (AB S)[14]
16) N N dimethyl *meta* phenylenediamine[c)] + N N dimethyl *para* phenylenediamine [d)] – AB for 18 hours/30 min (DI AB)[15]
17) AB post mild acid hydrolysis[16]
18) The bial reaction[17]
19) Aqueous mercuric bromphenol blue staining[18] (MBPB)

The following *blocking reactions* were used (table 2)

1) AA and AB post sulfation with sulfuric acid[19]
2) Phenylhydrazine blockade followed by PAS (PAPS)[5]
3) The Fisher Lillie methylation blockade for 4 hours at 37° C and 60° C followed by AA AB and PAS and saponification followed by AA AB and PAS[14]

Enzyme digestion was performed with the following enzymes and the stainings 1 4 6 9 10 11 12 13 14 16 and 19 were applied after the enzyme exposition (table 3) The solutions and concentrations were *according to Quintarelli*[12]

1) Pepsin[e)] for 2 hours at 37° C
2) Papain[f)] for 2 hours at 37° C after 30 min preheating at 37° C

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a) Diastase 2800E/g Merck Darmstadt no 3013
b) Merck Darmstadt no 1273
c) K & K Laboratories Inc Plainview New York
d) Eastman *Organic Chemicals Rochester 3* New York
e) Merck Darmstadt no 7192
f) Merck Darmstadt no 7144

3) Lysozyme[g] for 24 hours at 37° C.
4) Testicular hyaluronidase[h] for 5 hours at 37° C
5) Protease free *Vibrio cholerae* neuraminidase[i] at pH 5,5 every 6 hours for 24 hours at 35° C.

Control sections were incubated in buffer solutions without enzymes for the same time and at the same temperature

Results

The staining reactions were identical in glands removed post mortem and during operation and in the differently fixed sections although the CPC fixatives are claimed to preserve especially well the acid glycosaminoglycans [9] Frozen sections gave the same results as paraffin embedded sections

In the tables the staining reactions are graded arbitrarily from – → ++++

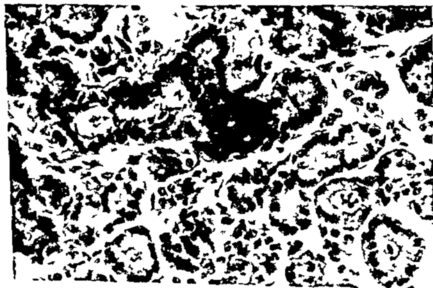


Fig 1
The periodic acid Schiff reaction after McManus following diastase hydrolysis CPC fixation. The granular structure of the cytoplasm is seen (× 450)

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g) Sigma Chem Corp no 105B3,00
h) Fluka AG Switzerland no 403019
i) Behringwerke Marburg Lahn no _0 61

immediately fixed in 4% buffered neutral formaldehyde for 24 hours Lillie s ethanol formalin acetic acid[3] for 24 hours both at 4° C as well as 4% formalin containing 0 5 per cent cetylpyridinium chloride (CPC)[4] at room temperature for 24 hours

In another two cases frozen sections of tissue removed during operation were stained directly

Routine paraffin technic was employed in the other instances From each gland about 65 sections were made

Deparaffinized hydrated sections were stained in the following ways (table 1)

1) The periodic acid Schiff reaction (PAS)[5, 6]
2) PAS following diastase[a)] hydrolysis at 37° C for 60 min[3]
3) 0 5 per cent aqueous toluidine blue O[b)] for 20 min at pH 0 9 1 42 1 99 3 4 and 5 0 (TBL)
4) 0 1 per cent TBL in 30 per cent ethanol[7] at the same pH ranges
5) 0 1 per cent azure A for 10 min at the same pH ranges as for TBL (AA)
6) TBL and AA after oxidative deamination with ninhydrin for 30 min at 37° C[8]
7) Methylene blue extinction[9]
8) Alcian blue 8 GS (AB)[10]
9) 0 5 per cent AB 8 GX in 3 per cent acetic acid[11]
10) Colloidal iron stain (Hale s reaction) (CI)[11]
11) AB and CI both in combination with the Feulgen Rossenbeck reaction for DNA (AB F CI F)[12]
12) AB 8 GX PAS[11]
13) CI PAS[11]
14) Aldehyde fuchsin AB (AF AB)[13]
15) AB Safranin O (AB S)[14]
16) N N dimethyl *meta* phenylenediamine[c)] + N N dimethyl *para* phenylenediamine [d)] – AB for 18 hours/30 min (DI AB)[15]
17) AB post mild acid hydrolysis[16]
18) The bial reaction[17]
19) Aqueous mercuric bromphenol blue staining[18] (MBPB)

The following *blocking reactions* were used (table 2)

1) AA and AB post sulfation with sulfuric acid[19]
2) Phenylhydrazine blockade followed by PAS (PAPS)[3]
3) The Fisher Lillie methylation blockade for 4 hours at 37° C and 60° C followed by AA AB and PAS and saponification followed by AA AB and PAS[14]

Enzyme digestion was performed with the following enzymes and *the stainings* 1 4 6 9 10 11 12 13 14 16 and 19 were applied after the enzyme exposition (table 3) The solutions and concentrations were according to Quintarelli[12]

1) *Pepsin*[e)] *for 2 hours at 37° C*
2) Papain[f)] for 2 hours at 37° C after 30 min preheating at 37° C

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f) Merck Darmstadt no 7144

3) Lysozyme[g] for 24 hours at 37° C.
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Results

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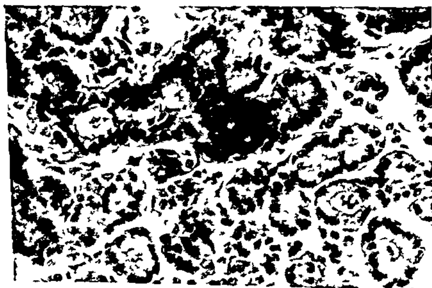


Fig 1
The periodic acid Schiff reaction after McManus following diastase hydrolysis CPC fixation The granular structure of the cytoplasm is seen (× 4 0)

g) Sigma Chem Corp no 105B3 00
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i) Behringwerke Marburg Lahn no 20761

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Deparaffinized hydrated sections were stained in the following ways (table 1):

1) The periodic acid Schiff reaction (PAS)[5, 6]
2) PAS following diastase[a)] hydrolysis at 37° C for 60 min.[3]
3) 0.5 per cent aqueous toluidine blue O[b)] for 20 min. at pH 0.9, 1.42, 1.99, 3.4 and 5.0 (TBL)
4) 0.1 per cent TBL in 30 per cent ethanol[7] at the same pH ranges
5) 0.1 per cent azure A for 10 min. at the same pH ranges as for TBL (AA)
6) TBL and AA after oxidative deamination with ninhydrin for 30 min. at 37° C[8]
7) Methylene blue extinction[9]
8) Alcian blue 8 GS (AB)[10]
9) 0.5 per cent AB 8 GX in 3 per cent acetic acid[11]
10) Colloidal iron stain (Hale's reaction) (CI)[11]
11) AB and CI both in combination with the Feulgen Rossenbeck reaction for DNA (AB-F, CI-F)[1]
12) AB 8 GX-PAS[11]
13) CI-PAS[11]
14) Aldehyde fuchsin-AB (AF-AB)[13]
15) AB-Safranin O (AB-S)[14]
16) N,N-dimethyl *meta* phenylenediamine[c)] + N,N-dimethyl *para* phenylenediamine[d)] – AB for 18 hours/30 min. (DI-AB)[15]
17) AB post mild acid hydrolysis[16]
18) The bial reaction[1]
19) Aqueous mercuric bromphenol blue staining[18] (MBPB)

The following *blocking reactions* were used (table 2):

1) AA and AB post sulfation with sulfuric acid[19]
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3) The Fisher-Lillie methylation blockade for 4 hours at 37° C and 60° C followed by AA, AB and PAS, and saponification followed by AA, AB and PAS[14]

Enzyme digestion was performed with the following enzymes and the stainings 1, 4, 6, 9, 10, 11, 12, 13, 14, 16 and 19 were applied after the enzyme exposition (table 3). The solutions and concentrations were according to Quintarelli[1].

1) Pepsin[e)] for 2 hours at 37° C
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Staining reactions without blocking or enzyme treatment (table 1)

The periodic acid Schiff reaction (PAS) without and after diastase hydrolysis was very strong and revealed in high magnification closely packed granules in the cytoplasm (fig 1)

Toluidine blue (TBL) and azure A (AA) at various pH showed constantly orthochromasia Oxidative deamination did not change this Sulfation gave no metachromasia (table 2) In large areas on the contrary the stainings with Alcian blue (AB) and AA were totally abolished while scattered orthochromatic granules were seen centrally in a few acini The unstained areas were not glandular tissue destroyed by the strong acid as the glandular tissue in its entirety could be demonstrated by subsequent staining with hematoxylin eosin.

Methylene blue staining was abruptly diminished between pH 3 5 and pH 3 0 while a weak blue color peripherally in the acini remained between pH 3 0 and pH 2 0 At lower pH no color was seen

AB and colloidal iron (CI) stained the cytoplasm strongly but the intensity was a little higher peripherally

The combined AB and CI PAS technic gave a mixture of blue and red so that the impression was a purple color (fig 2 A) The sequences of aldehyde fuchsin AB (AF AB) and AB safranin O (AB S) showed preponderance of blue while a rather weak purple AF and a weak yellow red S staining were located peripherally in the cytoplasm The high iron diamine stain (DI) in

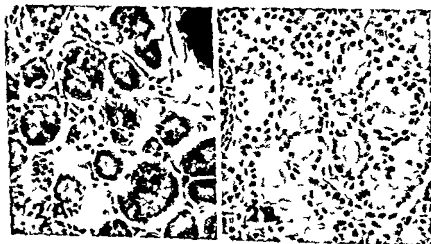


Fig 2 A
Alcian blue staining after Lison Formaldehyde fixation. Control section (× 275)

Fig 2 B
AB following mild acid hydrolysis for 9 hours showing the diminished staining (× 275)

Table 1

Staining reactions without blocking or enzyme treatment

Method of staining		Staining reaction
PAS		+++
PAS post diastase		++ (+)
TBL and AA pH 0.9–5		orthochromasia
TBL and AA post deamination pH 0.9–5		orthochromasia
Methylene blue extinction	pH 0.5	–
	– 1.0	–
	– 2.0	–
	– 3.0	(+)
	– 3.5	++
	– 4.0	++
	– 5.0	+++
AB		+++
CI		+++
AB – PAS		++ *) ++ (mixture of colours)
CI – PAS		++ *) ++ (mixture of colours)
AF – AB		+ *) +++
AB – S		+++*) +
DI – AB		+ *) +++
AA and AB post mild acid hydrolysis	1 h	++
	2 h	+
	3 h	+
	4 h	(+)
Bial reaction		++
MBPB		++

Symbols Staining method symbols See material and methods

– = no staining
(+)⟶ ++++ = degree of staining
*) Upper row Reactivity of the first dye in the sequence
Lower row Reactivity of the second dye in the sequence

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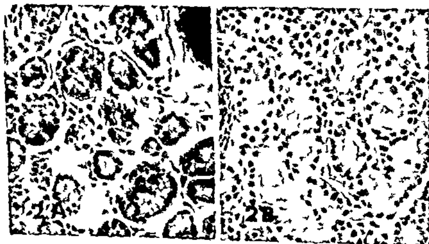


Fig 2 A
Alcian blue staining after Lison Formaldehyde fixation Control section (× 2 5)

Fig 2 B
AB following mild acid hydrolysis for 6 hours showing the diminished staining (× 275)

combination with AB gave a predominance of blue but a weak blackish blue in the periphery

Mild acid hydrolysis for 2 hours gave a diminished AB staining (fig 2 A B) After 4 hours the staining was still present but further reduced

The bial reaction gave the cytoplasm a diffuse orange color The tissue structure however was difficult to preserve and the color disappeared in hours

Mercuric bromphenol blue gave relatively weak diffuse blue color stronger in the connective tissue strands than in the acini where a fine granular structure could be distinguished

Blocking reactions (table 2)

The phenylhydrazine blockage followed by PAS (PAPS) gave a little increased red staining in relation to control sections

Methylation at 60° C weakened the PAS reaction considerably (fig 3 A B) but the color was restored by saponification Methylation at 37° C gave no significant change

After methylation at 60° C the AA and AB stainings were totally abolished and the *stainability was not restored* by saponification At 37° C the color intensity was diminished but never abolished Saponification did not restore the color (fig 4 A B C)

Table 2
Blocking reactions

Method of staining		*Staining reaction*
PAPS		+++ (+)
AB and AA post sulfation		weak orthochromasia
Methylation 37° C/4 h	PAS	++
	AA	+
	AB	+
Saponification (37°)	AA	+
	AB	+
Methylation 60° C/4 h	PAS	+
	AA	-
	AB	-
Saponification (60°)	PAS	+ (+)
	AA	
	AB	-

Symbols See table 1



Fig 3 A
The periodic acid Schiff reaction after McManus Formaldehyde fixation Control section (× 275)

Fig 3 B
PAS reaction after the Fisher Lillie methylation blockade at 60° C for 4 hours The weakened reaction shows a faint granular structure (× 275)

Staining reactions after enzyme treatment (table 3)

The PAS reaction was unchanged after incubation with all the used enzymes Especially the neuraminidase treatment gave no significant diminished coloring The orthochromasia did not change The neuraminidase treated sections showed only weak orthochromatic staining

Pepsin and papain digestion increased the blue color by staining with AB and CI separately and combined with PAS Especially these dye sequences gave now a deep blue color instead of a purple (fig 5 A B)

Lysozyme and hyaluronidase treatment gave no change in stainability and pepsin papain lysozyme or hyaluronidase did not change the AF AB or DI AB stainings

The most significant change of stainability showed the neuraminidase treated sections The AB and CI bindings were markedly diminished (fig 6 A B) giving in combination with PAS a red color (fig 7 A B) The combined AF AB procedure gave increased violet color and now more diffusely in the cytoplasm The DI staining was not increased but the AB staining in the sequence was markedly weakened

combination with AB gave a predominance of blue but a weak blackish blue in the periphery

Mild acid hydrolysis for 2 hours gave a diminished AB staining (fig 2 A B) After 4 hours the staining was still present but further reduced

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Table 2
Blocking reactions

Method of staining		Staining reaction
PAPS		+++ (+)
AB and AA post sulfation		weak orthochromasia
Methylation 37° C/4 h	PAS	++
	AA	+
	AB	+
Saponification (37°)	AA	+
	AB	+
Methylation 60° C/4 h	PAS	+
	AA	-
	AB	-
Saponification (60°)	PAS	+ (+)
	AA	
	AB	-

Symbols See table 1

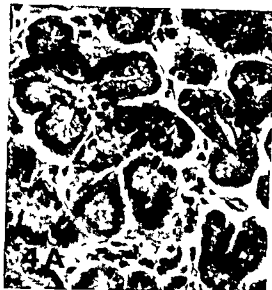


Fig 4 A
Azure A (0 1 per cent) for 10 minutes at pH 3 Formaldehyde fixation
Control section (× 275)



Fig 4 B
AA after the Fisher Lillie methylation blockade at 37° C
The color intensity is diminished (× 275)

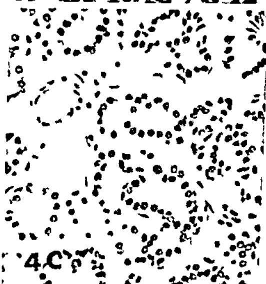


Fig 4 C
AA after the Fisher Lillie methylation blockade at 60° C
The cytoplasmic staining is totally abolished (× 275)



Fig 4 A
Azure A (0 1 per cent) for 10 minutes at pH 3 Formaldehyde fixation
Control section (× 275)



Fig 4 B
AA after the Fisher Lillie methylation blockade at 37° C
The color intensity is diminished (× 275)

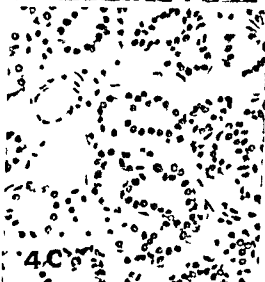
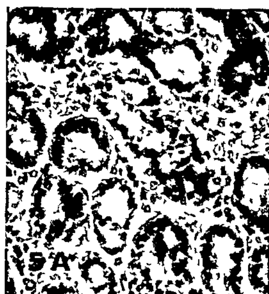


Fig 4 C
AA after the Fisher Lillie methylation blockade at 60° C
The cytoplasmic staining is totally abolished (× 275)


5 A

5 B

6 A

6 B

7 A

7 B

Pepsin and papain treatment weakened the MBPB staining of the acini showing a more diffuse blue of the cytoplasm

Discussion

The orbital lacrimal gland of rodents examined by the PAS reaction [21, 22] showed granules in the cytoplasm of acinar cells comparable to the granules in the parotid gland a serous gland A relation was found between the intensity of the PAS reaction and the secretory function [3] No ^{35}S incorporation was found in the lacrimal acini of mice indicating a lack of sulfated MS in this gland [4]

In Mammals (horse ox sheep pig dog) there are great differences between the MS of the lacrimal gland [5, 26]

The orbital lacrimal gland of man has been examined only by the PAS reaction[1] revealing strongly positive granules in the cytoplasm as also found by us (fig 1)

No histochemical method is specific for demonstration of mucopolysaccharides (MPS) neutral or acid A combination of various methods however gives an impression of the composition and localization of possible MS in tissues

Our examination showed that the human orbital lacrimal gland did not

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Fig 5 A

The combined colloidal iron PAS staining after Mowry showing a mixture of blue and red CPC fixation (× 275)

Fig 5 B

The CI PAS sequence after papain digestion for 2 hours at 37° C The Hale positive material is markedly enhanced (× 275)

Fig 6 A

AB staining after Lison Formaldehyde fixation. Control section (× 275)

Fig 6 B

AB staining after *Vibrio cholera* neuraminidase treatment every 6 hours for 24 hours at 38 C The alcianophilic material is markedly removed (× 275)

Fig 7 A

The CI PAS sequence after Mowry Formaldehyde fixation Control section (× 275)

Fig 7 B

The CI PAS sequence after *Vibrio cholerae* neuraminidase treatment every 6 hours for 24 hours at 38 C The Hale positive material is markedly removed (× 275)

Table 3
Staining reactions after enzyme treatment

Method of staining	pepsin	papain	lysozyme	hyaluronidase	neuraminidase
PAS	++	++	++	++	++
TBL	orthochromasia	orthochromasia	orthochromasia	orthochromasia	weak orthochromasia
TBL and AA after deamination pH 0.9–5	orthochromasia	orthochromasia	orthochromasia	orthochromasia	weak orthochromasia
AB	++++	++++	+++	+++	(+)
CI	++++	++++	+++	+++	(+)
AB – PAS	+++ *) +	+++ *) +	++ *) ++	++ *) ++	(+) *) ++
CI – PAS	+++ *) +	+++ *) +	++ *) ++	++ *) ++	(+) *) ++
AF – AB	+ *) +++	+ *) +++	+ *) +++	+ *) +++	++ *) +
DI – AB	+ *) +++	+ *) +++	+ *) +++	+ *) +++	+ *) (+)
MBPB	+	+	++	++	++

Symbols See table 1

contain metachromatic substances in a histochemically demonstrable amount The lack of metachromasia at low pH could be caused by a competitive cationic effect by the presence of proteins but oxidative deamination[8] did not change the orthochromasia Sulfation may induce an artificial metachromasia[27] Orthochromatic MS in some serous glands however do not change their orthochromasia after sulfation[14] In our material sulfation abolished the stainability with AA and AB apart from a scant orthochromasia in small areas The present authors are inclined to explain this as a consequence of acid hydrolysis by the sulfuric acid whereby the AA and AB stainable substances are removed Especially sulfated MS give β – metachromasia but not all[8] Metachromasia can also be induced by certain non sulfated MS although orthochromasia is more common[29, 30] Strongly acid sulfated MS are chromotrope and hyaluronidase sensitive[31] As neither of these qualities were found these substances seem not to be present in the gland

Apart from the centrally located deep blue color application of an AF AB and an AB S sequence gave a light staining peripherally in the cytoplasm purple and red respectively A DI AB sequence stained the periphery faintly blackish blue indicating the presence of a mixture of carboxyl containing mucins and sulfomucins[15] After treatment with neuraminidase the purple color was increased by application of an AF AB sequence as alcianophilic material was removed The above dye sequences allow a differentiation between sulfated and non sulfated MPS[11, 29] and so indicate a content of acid MPS with other acid groups than carboxyl groups

Carboxyl containing polysaccharides are stained by AB and CI[11] Carboxyl groups are probably not dissociated at a pH lower than 3 5 to 3 0 The result of the methylene blue extinction test and the unchanged AB and CI basophilia after treatment by hyaluronidase indicate presence of mainly acid MS other than hyaluronic acid

Neutral MPS are PAS positive and diastase resistant No agreement exists upon the PAS reactivity of sialic acid[12] Most authors however agree that the 1–2 glycol groups of sialic acid can be oxidized by periodic acid and stained by Schiff s reagent In the same way a reduction of the PAS reactivity after methylation and neuraminidase treatment should be caused by removal of sialic acid MS containing low concentration of sialic acid but high concentration of hexosamine fucose and galactose will not change their PAS reactivity by the above procedures In our material the PAS reactivity did not change after neuraminidase but was reduced after methylation at 60° C (fig 3) This confusing fact may be explained by a possible removal of sialic acid by the neuraminidase but remaining of other PAS positive substances in high concentration so that a visible change of color did not take place The more unspecific methylation may block OH groups also in other substances than sialic acid with the consequence that the reaction is reduced

Mild acid hydrolysis (pH 2.5)[16] removed the basophilia after 2 hours at 80° C (fig 2) but still after 3 and 4 hours some basophilia was left According to several authors[16, 3, 33, 34, 35] sialic acid is split off by this procedure The remaining basophilia may in the opinion of the present authors be ascribed to the presence of weakly acid sulfated MPS which according to *Spicer*[30] have extinction values between pH 1.5 and pH 3.0 This is consistent with the result of the extinction test (table 1) showing light basophilia at pH 3.0 but practically none at lower pH

PAPS staining entailed strong red color of the acini perhaps a little stronger than a control PAS staining

Phenylhydrazine blocks aldehydes and eliminates the PAS staining of neutral MS while siolomucins are colored[16]

Methylation at 60° C (active methylation) abolished the AB and AA staining (fig 4) and reduced the PAS reaction According to *Quintarelli*[1] this is due to a hydrolytic effect of acid methanol at 60° C for 4 hours so that alcianophilic and azurophilic substances are split off This effect is much stronger than the effect of mild acid hydrolysis and mild methylation (methylation at 37° C) These procedures only suppressed basophilia The remaining basophilia may in our opinion be ascribed to weakly acid sulfated MS[10] That saponification did not restore basophilia may be caused by an extracting and not an unblocking effect of the demethylation medium which is strongly alkaline [1]

According to *Carlo*[1] the bial reaction modified for histological use is specific for metoxy- and N acetylneuraminic acid A false positive staining of glycolipids cannot be ruled out however[3] This method proved not valuable in our hands

The combined staining procedures after proteolytic enzyme treatment on the contrary were very significant The basophilia was markedly increased (fig 5) indicating a liberation of anion groups bound to protein The decrease of the MBPB coloring after proteolysis also point at a protein structure of the cytoplasmic MS and granules

The strong neuraminidase effect (fig 6 and 7) was very significant and is no doubt the most specific procedure for demonstrating sialic acid histochemically

Conclusively the MS of the acini of the orbital part of the human lacrimal gland are characterized by being orthochromatic strongly PAS and PAPS positive strongly alcianophilic and Hale positive to have methylene blue extinction values mainly between pH 3.5 and pH 3.0 to be hyaluronidase resistant and strongly neuraminidase sensitive and partly protein bound These findings point at a high content of sialic acid Further mainly localized peripherally in the cytoplasm are probably small amounts of weakly acid sulfated MPS

Comparison with other glands investigated thoroughly showed a similarity in the histochemical pattern between the human lacrimal gland and the parotid gland of the dog[12] a serous gland with an identical morphology and with the lacrimal gland of the horse[5 20 38] In this gland a biochemical analysis showed a high concentration of sialic acid[38]

Abstract

The mucosubstances of the acini of the human orbital lacrimal gland were examined by applying a battery of histochemical methods to normal gland tissue The material was obtained during operation and postmortally from persons 20–50 years old

The mucosubstances of the acini were found to be orthochromatic strongly PAS and PAPS positive strongly alcianophilic and Hale positive to have methylene blue extinction values mainly between pH 3 5 and pH 3 to be hyaluronidase resistant and highly neuraminidase sensitive and partly protein bound In the periphery of the cytoplasm were found aldehyde fuchsin safranin and high iron diamine positive material in small amounts

The findings indicate a high amount of sialic acid and small amounts peripherally of weakly acid sulfated mucopolysaccharides

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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MUCOSUBSTANCES OF THE ACINI OF THE HUMAN LACRIMAL GLAND (ORBITAL PART)

II Biochemical identification

BY

IENS FALBE HANSEN OVE A JENSEN and JUDITH KAROSSA DEGN

In the serous lacrimal gland of the horse the presence of sialic acid in high concentration was demonstrated by Aureli Ferri & Castellani[1] The equine lacrimal gland is in many respects similar to the orbital part of the human lacrimal gland and since histochemical studies of the latter also indicated the presence of mucosubstances containing sialic acid[2] the need for a chemical confirmation and identification became obvious

Material and Methods

Human lacrimal glands (orbital part) were removed 12 18 hours after death and freed from fat and connective tissue All the glands were from the age group 20–50 years Immediately after the removal the glands were frozen to

This investigation was supported by a grant from Landsforeningen til Kræftens Bekæmpelse

–20° C and kept at this temperature until a sufficient amount had been collected

Extraction

15 7 g of lacrimal gland (wet weight) were homogenized for 2 3 minutes in a Waring blendor with 33 ml ice cold destilled water The homogenate was left overnight at 4° C under constant stirring After the residue had settled the supernatant (I) was decanted off and left at 4 C

The residue contained several comparatively large pieces of tissue which were collected and extracted twice with 17 ml destilled water over 2 days The extraction was carried out at 4 C under constant stirring These two extracts (II and III) were combined with extract I

Isolation of polysaccharide

The isolation was carried out according to a method outlined by Balazs[3] 2 2 ml 1 % cetyl pyridinium chloride (CPC) were added dropwise to the extract until a precipitate started to form The extract was left overnight at 4° C The next day a powdery white precipitate had formed After centrifugation for 30 *min* at 3000 × g in a refrigerated MSE centrifuge the supernatant was decanted off and the sediment (a) was kept at 4 C

The supernatant was slowly mixed with 2 ml 1 % CPC and left overnight at 4 C By that time a new precipitate (b) had formed and centrifugation was repeated as previously The sediments (a) and (b) were combined and dissolved in 50 ml icecold 1 M $MgCl_2$ As the dissolution was only partial the sample was centrifuged at 15 000 × g for 30 min in a refrigerated MSE *centrifuge and* after the supernatant had been decanted off *the sediment* was mixed again with 25 ml 1 M $MgCl_2$ Centrifugation was repeated as previously and the two supernatants were combined 270 ml cold 100 % ethanol were added to the 55 ml supernatant First there was an obvious increase *in viscosity* and then a sticky white *precipitate appeared* The solution was centrifuged for 30 min at 3000 g in a *refrigerated* MSE centrifuge The supernatant was discarded and the sediment was dried in a vacuum dessicator at 4 C The dried material was redissolved in 25 ml cold destilled *water As the* solution was milky it was centrifuged at 4 C *in* a Beckmann preparatory ultracentrifuge at 60 000 × g *for 1 hour* The clear supernatant was freezedried Yield 0 276 g

The dry material was redissolved *in water* and as addition of $AgNO_3$ revealed the presence of Cl probably M_gCl_2 ethanol was added to a final concentration of 80 % The *resulting* precipitate was centrifuged at 7000 × g for 30 min redissolved in destilled water and dialyzed *in a* Visking dialysis bag overnight at 4 C against 200 volumes of destilled water The solution was

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The dry material was redissolved in water and as addition of $AgNO_3$ revealed the presence of Cl probably MgCl ethanol was added to a final concentration of 80 % The resulting precipitate was centrifuged at 7000 × g for 30 min redissolved in destilled water and dialyzed in a Visking dialysis bag overnight at 4 C against 200 volumes of destilled water The solution was

freezedried and although there was an accidental loss of material enough was saved to permit analysis

Determination of hexosamine

After hydrolysis with 8 M HCl for 3 hours at 95° C the hexosamine content was determined according to Swann & Balazs[4]

Determination of methylpentose

The methylpentose content was determined according to Dische & Shettles[5] Fucose was used as standard

Determination of Hexose

The total hexose content was determined by the orcinol method of Vasseur[6]

Determination of sialic acid

After hydrolysis for 1 hour at 80° C with 0 1 N HCl the sialic acid content was determined by the thiobarbituric acid method of Aminoff[7]

Determination of protein

Protein determination was carried out according to the method of Lowry et al[8]

All analyses were carried out as duplicate determinations The spectrophotometric readings were performed with a Zeiss PMQ II spectrophotometer

Results

The results of the analyses are given in Table 1 The total amounts to more than 100 % This is probably caused by a too high protein reading Unfortunately this could not be verified by a nitrogen determination as there was no more material left

Discussion

Sialic acid was originally isolated from mucinous glands and its presence in serous glands was not demonstrated till many years later[1] The latter invest

Table 1
Percentage distribution of various compounds in mucoid substance isolated from human lacrimal gland

Hexosamine	13 %
Hexose	20 %
Methylpentose	1 %
Sialic acid	40 %
Protein	46 %

igations showed a high content of sialic acid in the equine lacrimal gland Our studies reveal that this is also true of the human lacrimal gland Since a possible relation between sialic acid and positive periodic acid Schiff reaction has been reported[9] it seems justifiable to assume that the sialic acid containing substance is located in the dense granules of the acinous cells of the gland[2]

The relative amount of sialic acid is higher than the figures given by Tsuiki et al[10] for bovine submaxillary mucin It is possible that the hexose like in suomaxillary mucin is d galactose but this has not been verified The ratio between methylpentose and sialic acid is more in accordance with the figures usually given for glycoproteins[11] than with the figures given for epithelial mucins

We have no data concerning the homogeneity of the purified substance

The functional significance of this sialic acid containing substance is unknown but at least two possibilities may be considered It may be a secretory product present in the tear liquid which accordingly is less serous than generally believed In parotid saliva the presence of a mucoprotein has been demonstrated but this substance contains more fucose than sialic acid[12]

The other possibility is that it forms part of the membranes of cellular organelles having an influence on potassium transport and protein liberation from the cell[13]

Acknowledgement

W wish to thank Dr E A Balazs for h s many helpful suggestions

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MICROSPECTROPHOTOMETRIC STUDIES OF PIGMENT CONTAINING CELLS IN THE HUMAN EYE

BY

SØREN JENSEN

Diktyoma and epithelioma of the retina i e embryonic and adult medulloepithelioma respectively are considered to be derived from the neural tube while uveal melanomas are considered to be derived from the neural crest This assumption is supported int al on the size of the melanin granules the retinal ones being larger than the uveal In some cases however it may be impossible to decide and furthermore there are apparently transitions between tumours derived from the tube and the crest For instance as far as *some melanin* containing cells are concerned e g clump cells of the iris we still do not know whether they are of retinal or uveal origin Accordingly it would be of great theoretical as well as practical importance to arrive at a method by which it would be possible in histological sections to differentiate between melanin from the various retinal and uveal parts of the eye

The object of the present study was to investigate whether microspectrophotometry is applicable for this purpose The study was based upon a finding made by *Pakkenberg* (1966) In connection with his microspectrophotometric studies of pigment cells in the substantia nigra in parkinsonism this author carried out some investigations of ocular pigment He found that pigment from the retina, choroid and iris had an absorption maximum around 430 nm while some of the pigment containing cells from the ciliary body had a maximum around 480 nm and others around 430 nm

Abstract

A substance rich in sialic acid was isolated from human lacrimal glands The substance also contained hexosamine hexose methylpentose and protein It seems probable that the substance is located in PAS positive granules present in the acinous cells of the gland The possible functional significance of the substance is briefly discussed

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The object of the present study was to investigate whether microspectrophotometry is applicable for this purpose The study was based upon a finding made by *Pakkenberg* (1966) In connection with his *microspectrophotometric* studies of pigment cells in the substantia nigra in parkinsonism this author carried out some investigations of ocular pigment He found that pigment from the retina choroid and iris had an absorption maximum around 430 nm while some of the pigment containing cells from the ciliary body had a maximum around 480 nm and others around 430 nm

Method

The apparatus was that described by *Palkenberg* (1960) consisting of an Ortholux microscope (Leitz) combined with a Photovolt multiplier photometer (Fig 1) The multiplier phototube is placed 40 cm above the eyepiece This

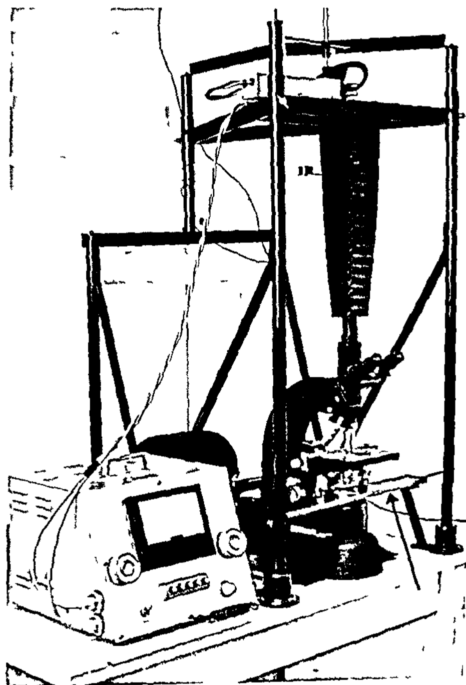


Fig 1
Microspectrophotometer The arrow shows the interference wedge

gives a magnification of 2750 × It is mounted on rails so that it may be pushed from side to side In the centre of the rails in the optical axis of the microscope there is a circular disc of frosted glass and in the centre of this disc a circle diameter 4 mm is engraved This field corresponds to an area in the cell having a diameter of 1 32 μ In a mirror placed above the rails the examiner can see the disc while selecting the area to be measured The photo tube has an aperture corresponding to the circle on the frosted glass disc. During the measurements the phototube is placed so that this aperture and the circle on the frosted glass disc are exactly above each other Beneath the condenser of the microscope there is an interference wedge provided with a ratchet device so that it may be fixed in 24 positions each corresponding to a given wavelength The interference wedge is in a metal casing with a 2 mm slit for the passage of light The light source is a tungsten lamp 12 V 6 A

The studies were done on unstained deparaffinized 8 μ thick sections from a normal eye and from eyes with various tumours Measurements of a total of 45 cells were made at four sites in each cell (Table I) The results were plotted in a coordinate system the wavelength as the abscissa and the extinction as ordinate The extinction was not read directly from the photometer but calculated as $-\log\frac{\alpha}{b1}$ where α is the value read when light of a given wavelength passes through the area of the measurement and b1 the blank value read when light of the same wavelength passes through the section just outside the cell The shape and peak of the curves were the same for each cell whereas the level of the curves varied according to the concentration of pigment in the measured area a higher concentration of pigment giving a flatter curve The examples given here are typical average curves

Results

Fig 2 illustrates curves from melanocytes of the iris stroma Measurement of clump cells in the stroma and of cells in the anterior layer of the iris pigment epithelium gave similar curves All the curves show a maximum around 430 nm Measurement of the cells with a very high pigment content in the posterior layer of the iris pigment epithelium gave flat curves without a maximum

Fig 3 presents curves from uveal melanocytes of the ciliary body In these curves too the absorption maximum is around 430 nm The same result was obtained when measuring the pigment epithelium of the ciliary body only the curves were flatter due to a higher concentration of pigment

Fig 4 shows curves from the retinal pigment epithelium The absorption maximum is around 430 nm

Table I

Results of Microspectrophotometry of Pigmented Cells from a Normal Eye and from Eyes with with Pigmented Tumours

Location of Cells	Number of Cells	Absorption maximum
Normal eye (Oft pat lab No 289/62)		
Iris (melanocytes clump cells and pigment epithelium)	10	About 480 nm
Ciliary body (malanocytes and pigment epithelium)	15	About 480 nm
Choroid (*melanocytes*)	9	*About 480 nm*
Retina (pigment epithelium)	4	About 480 nm
Tumours		
Melanoma of the iris (Oft pat lab No 158/68)	2	About 480 nm
Malignant melanoma of the choroid (Oft pat lab No 286/68b)	2	About 480 nm
Malignant diktyoma of the ciliary body (*Oft pat lab No 2[illegible]6/68*)	2	About 480 nm
benign epithelioma of the ciliary body (Oft pat lab No 489 68)	1	About 480 nm
Teratoma of the orbit (Oft pat lab No 619/67)	2	*About 480 nm*
Siderosis of the ocular bulb (Oft pat lab No 261/68)	4	About 480 nm

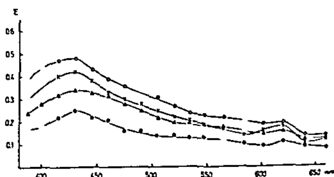


Fig 2

Spectral curves from melanocytes of the iris stroma

Figs 5 6 and 7 give curves for tumour cells of an iris melanoma a malig nant diktyoma and a benign pigmented epithelioma of the ciliary body In these cases too the absorption maximum is around 480 nm

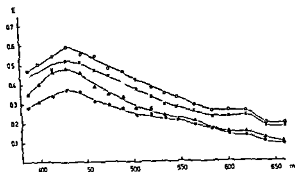


Fig 3
Spectral curves from uveal melanocytes of the ciliary body

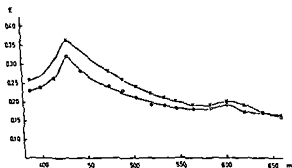


Fig 4
Spectral curves from the retinal pigment epithelium

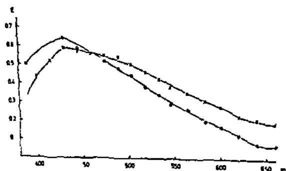


Fig 5
Spectral curves of tumour cells in an iris melanoma

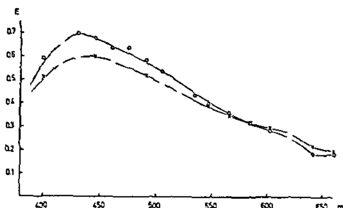


Fig 6
Spectral curves of tumour cells in a malignant diktyoma

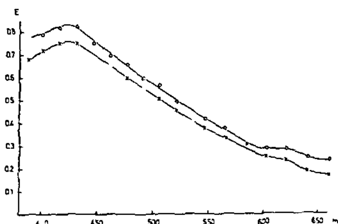


Fig 7
Spectral curves of tumour cells in a benign pigmented epithelioma from the ciliary body

In all figures most of the curves show besides a more or less marked secondary maximum around 620 nm

Discussion

Measurements of the spectral absorption of melanin have been reported several times *Caspersson* (1936) found maximum absorption in the long waved ultra

violet range while absorption in visible light was slight and from 250 300 nm entirely absent *Meyer Arendt* (1951) studying some of the late precursors of melanin found an absorption maximum in the ultraviolet range at 366 nm *Bayer* (1954) studying the absorption of melanin granules in visible light also found no absorption maximum here but an increasing extinction towards the short wave end of the measuring range On the other hand *Hesselbach* (1953) whose measurements were made on extracted pigment found an absorption maximum in the visible area of the spectrum at 450 nm

In the present study the spectral curves from pigment containing cells of a normal eye and from some pigment containing intra ocular tumours invariably showed an absorption maximum in the visible part of the spectrum around 430 nm

Thus the difference found by Pakkenberg in the absorption maximum between pigment containing cells in the ciliary body and in other parts of the eye could not be confirmed However Pakkenberg performed his measurements on only a few cells which could not later be identified and it could not be ruled out that the deviating cells were macrophages which had ingested iron containing pigment However when measuring such cells in an eye with siderosis the present author also found the absorption maximum to be around 430 nm (Table I) Accordingly the difference found by Pakkenberg was presumably accidental and microspectrophotometry does not appear to be applicable for making a distinction between melanin from the various parts of the eye

Summary

Pigment containing cells from a normal eye and from various pigment containing intra ocular tumours were studied microspectrophotometrically in the visible part of the spectrum Measurements were made on a total of 45 cells at four sites in each cell All the spectral curves showed an absorption maximum around 430 nm and the majority besides *a more or less* marked secondary maximum around 6?0 nm

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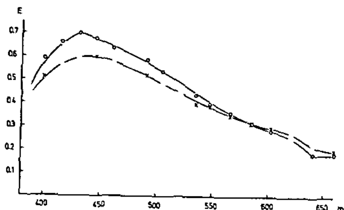


Fig 6
Spectral curves of tumour cells in a malignant diktyoma

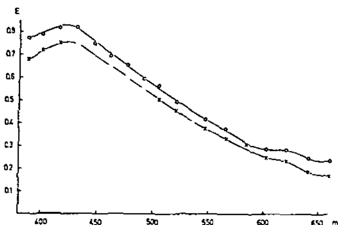


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Thus the difference found by Pakkenberg in the absorption maximum between pigment containing cells in the ciliary body and in other parts of the eye could not be confirmed However Pakkenberg performed his measurements on only a few cells which could not later be identified and it could not be ruled out that the deviating cells were macrophages which had ingested iron containing pigment However when measuring such cells in an eye with siderosis the present author also found the absorption maximum to be around 430 nm (Table I) Accordingly the difference found by Pakkenberg was presumably accidental and microspectrophotometry does not appear to be applicable for making a distinction between melanin from the various parts of the eye

Summary

Pigment containing cells from a normal eye and from various pigment containing intra ocular tumours were studied microspectrophotometrically in the visible part of the spectrum Measurements were made on a total of 45 cells at four sites in each cell All the spectral curves showed an absorption maximum around 430 nm and the majority besides a more or less marked secondary maximum around 620 nm

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the Eye Clinic
(Head professor G Karpe M D)
Karolinska sjukhuset Stockholm 60

CLINICAL ELECTRORETINOGRAPHY IN DETACHMENT OF THE RETINA

BY

G KARPE and I RENDAHL

Since 1946 electroretinography (ERG) has been used as a clinical routine method of examination at the Eye Clinic of Karolinska sjukhuset The total collected material now comprises about 5700 cases with normal or pathological eyes Of this number 1131 consist of completely normal and fully healthy eyes and 531 of eyes with detachment of the retina In this survey of the electroretinogram in retinal detachment in particular its practical usefulnes in clinical work will be considered

The normal cases forming the comparative material have recently been analyzed by *Peterson* (1968) whereas several collocations of retinal detachment have been made by *Rendahl* (cf 1961 1968)

Method of examination

The ERG examination is performed as a recording of the action potential from the total retina after stimulation by single short flashes of the patient s semi dark adapted eye (*Karpe* 1945 1967) The recording is made from each eye separately (Fig 1) After 4 5 technically satisfactory curves have been obtained from both eyes the type of the curve is determined (Fig 2) and the mean value of the b potential is calculated The recording is made with three different strengths of the stimulus i e 20 80 and 500 lux (Fig.3) The curve giving the highest b potential of them is chosen (*Karpe* & *Uulfing* 1962) A comparison is

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Fig 1
The arrangement of the leading off is ready

made between the two eyes – which might be informative in unilateral detachment of the retina – as well as with a normal series of patients of the same sex and age whose refraction is the same as that of the patient with detachment

The normal electroretinogram

The size of the b potential of the ERG varies with several circumstances The dark adaption and strength of light stimulus are the two most important factors which are standardized in the present method The b wave is however higher in women than in men and it decreases in a typical way with rising age and myopic refraction Consequently these factors must always be taken into account in the comparative material (cf *Peterson* 1968 and Table I)

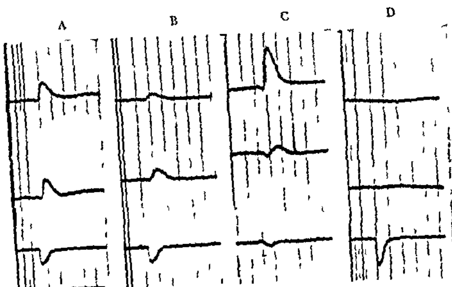


Fig 2

Electroretinogram curves of different types The curves 1 from the right eye 2 from the left eye 3 recording of the light stimulus Times 0 1 and 0 02 sec.
A Normal ERG in both eyes B Subnormal ERG in the right eye (1) with ablatio retinae small ERG but within normal limits in the left eye (2) C. Supernormal ERG negative ERG in an eye with thrombosis of the central retinal vein. D 1 and 2 Extinguished ERG in a case with bilateral retinitis pigmentosa

Case material

In most of the patients with detachment of the retina who attended the Clinic, the ERG was recorded on one or several occasions The present series consists of 274 patients with unilateral retinal detachment and 60 eyes with bilateral detachment (Table II)

The ERG in unilateral retinal detachment

In retinal detachment the b wave decreases and the ERG becomes subnormal or in some cases – i e in total detachment – extinguished in type (see Fig 2) This decrease in the b wave is primarily correlated to the extent of retinal detachment Thuse the greater the extent of retinal detachment in the fundus the lower is the b potential recorded on the average

It can however also be demonstrated that the decrease in the b potential is not only dependent on the size of the detached area but that it is also affected by a qualitative factor – namely to how great a degree the retina is damaged on detachment (Table III)



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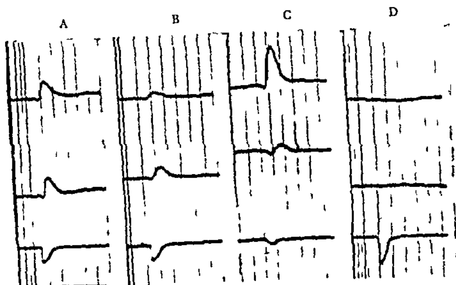


Fig 9

Electroretinogram curves of different types The curves 1 from the right eye 2 from the left eye 3 recording of the light stimulus Times 0 1 and 0 0? sec.
A Normal ERG in both eyes B Subnormal ERG in the right eye (1) with ablatio retinae small ERG but within normal limits in the left eye (2) C. Supernormal ERG ? negative ERG in an eye with thrombosis of the central retinal vein. D 1 and 2 Extinguished ERG in a case with bilateral retinitis pigmentosa

Case material

In most of the patients with detachment of the retina who attended the Clinic, the ERG was recorded on one or several occasions The present series consists of 4 patients with unilateral retinal detachment and 60 eyes with bilateral detachment (Table II)

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Table I

(After Peterson, 1968) The b potential in men aged 10 69 years

Age yrs	mV Mean	Limits including a certain percentage of normal cases (mV)		
		95 %	99 %	99 9 %
10 19	0 39	0 3–0 55	0 18–0 60	0 12–0 66
20 9	0 37	0 21–0 53	0 16–0 58	0 10–0 64
30–39	0 36	0 20–0 57	0 15–0 5	0 09–0 63
40–49	0 34	0 18–0 50	0 13–0.55	0 07–0 61
50–59	0 33	0 17–0 49	0 12–0.54	0 06–0 60
60–69	0 32	0 16–0 48	0 11–0 53	0 05–0.59

The b potential in women aged 10 69 years

Age yrs	mV Mean	Limits including a certain percentage of normal cases (mV)		
		95 %	99 %	99 9 %
10–19	0 42	0 26–0 58	0 21–0 63	0 15–0 69
0–29	0.39	0 23–0 55	0 18–0 60	0 12–0 66
30–39	0 41	0 25–0.57	0 20–0 62	0 14–0 68
40–49	0 44	0 28–0 60	0 23–0 6	0 17–0 71
0–59	0 3	0 19–0 51	0 14–0 56	0 08–0 62
60–69	0 35	0 19–0 51	0 14–0 56	0 08–0 62

1 If the b wave is more than 0 20 mV reattachment is as a rule attained after operation

2 When the b wave is 0 11 0 20 mV before operation reattachment can be expected in about 75 % of the cases

3 If there is a subnormal ERG with a b wave not exceeding 0 10 mV the operation can be expected to be succes ful in 50 % of the cases

The ERG of the fellow eye

In a series of 80 cases of idiopathic detachment (*Rendahl* 1961) the fellow eye was reported to be healthy at clinical examination In both non myopic and myopic fellow eyes it was demonstrated that the mean b potential was



Fig

The intensity of the stimulus light is re[illegible] Stan[illegible] intensities 0 50 and 500 lux

This is especially apparent when one studies the relation between the b wave recorded before operation and the possibility of the retina becoming reattached after it. Thus it is found that in detachment with about the same surface area the frequency of reattachment is greater in those cases which have a higher b potential before operation. Those who have on the contrary a greatly reduced b potential show a decreased possibility of firm reattachment. This implies that on recording of the ERG one can also obtain a rough estimate of the retina's viability which is correlated to the ability to reattach after operation.

Our experience based on 274 cases of operated unilateral detachment of the retina is the following

assumption is made that both eyes had about the same ERG before detachment these results indicate the existance of predisposing factors in some cases of idiopathic detachment factors which influence the results of operation

The ERG in bilateral retinal detachment

In retinal detachment localized degenerative changes are present in the retina and play a part in the origin of retinal tears In bilateral detachment it may reasonably be assumed that those changes are present in both retinae However it is interesting to note that in the bilateral cases in which the operation was successful the mean value of the b potential was lower than in unilateral retinal detachment (Table IV)

This leads one to assume that the degenerative changes are severer in character in bilateral than in unilateral detachment

On the other hand in the cases in which surgery was unsuccessful the amplitude of the b potential was on average higher as compared with the mean value of the b potential in the cases of unilateral detachment This supports the view that the degenerative changes are localized and do not involve the entire retina in bilateral detachment The difference with respect to prognosis in bilateral detachment is probably related to factors such as the size and number of tears and the co existance of pathological changes in the vitreous body

The ERG after reattachment

In most cases the ERG had been subnormal before operation and in this case material the b potential increased only negligibly after reattachment In cases where the FRG before operation had been extinguished however there was a particular tendency to an increase in the b potential after operation

The clinical value of ERG recording

We all know that a case of idiopathic detachment of the retina with a retinal hole only extremely seldom reattaches unless one has succeeded in closing the retinal hole by operation Consequently on principle operation of retinal detachment is almost indicated But in certain cases – e g in debilitated elderly persons or in cases in which operation has previously been unsuccessful – one must nevertheless give up and refrain from a new operation It is in these cases that some guidance can be obtained by recording the ERG If the ERG proves to be extinguished the likelihood of achieving reattachment by operation is considerably decreased in comparison to that in cases in which the b wave is fairly well preserved In practice recording of the ERG has in fact been found to provide good guidance between operation and no operation in such cases of retinal detachment

Table II

The ERG in retinal detachment: survey of the case material

Retinal detachment	Op successful, no of eyes	Op successful but recurrent detachment	Op unsuccessful no of eyes
Unilateral	202	30	72
Bilateral	40	3	20
Juvenile cases (3–19 years of age)	18		6
Total	288		98

The main part of the remaining 145 cases have not been operated on (cf *Rendahl* 1961); in a few cases no ERG was recorded *before* operation.

Table III

Correlation between area of retinal detachment, b potential of the ERG before the operation and result of the operation

Extent of detachment	1/4 th	2/4 th	3/4 th	4/4 th
	n b pot mV	*n* b pot mV	*n* b pot mV	*n* b pot mV
Later op successful (202 eyes)	49 0.22	111 0.15	36 0.07	6 0.00
Later op unsuccessful (72 eyes)	8 0.13	39 0.05	17 0.03	8 0.01
Difference	0.083	0.072	0.031	0.006
Standard error	0.032	0.012	0.015	
t	2.59	6.00	2.07	
P	< 0.05	< 0.001	< 0.05	
Significanse	*	***	*	

lower in those cases where detachment of *other eye had been operated on with out success* than in a control group of patients *without detachment*. In the non-myopic group the mean b potential of the fellow eye was *0.05 mV lower*. If the

As a rule the diagnosis of retinal detachment is made with the help of the ophthalmoscope But in cases in which the transparency of the optical system is greatly reduced – and retinal detachment cannot therefore be diagnosed but cannot either be ruled out – the ERG recording can provide valuable guidance The type of curve is not specific to detachment and a diagnosis cannot be made only on the basis of the ERG Nevertheless as a complementary test to all other ophthalmological examinations recording of the ERG has proved to be of great practical value It is in fact used as a routine examination in all cases of suspected or established detachment of the retina at our Clinic

Summary

Since 1946 electroretinography (ERG) has been used as a clinical routine method of examination at the Eye Clinic of Karolinska sjukhuset In retinal detachment the ERG becomes subnormal However the decrease of its b potential is not only dependent on the size of the detached area but it also affected by a qualitative factor i e to how great a degree the retina is damaged on detachment This implies that on recording of the ERG one can also obtain a rough estimate of the retina s ability to reattach after operation as well as a guidance between operation and no operation in special cases of retinal detachment

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Table IV

The ERG in bilateral retinal detachment

Correlation between area of detachment mean b pot. before the operation and result of the operation

Extent of detachment

	0 1/4		1 2/4		2 3/4		3 4/4	
Bilateral retinal detachment	*n*	*b pot mV*	*n*	*b pot mV*	*n*	*b pot mV*	*n*	*b pot mV*
Later operation successful (40 eyes)	13	0 24	22	0 12	4	0 0,	1	0 00
Later operation unsuccessful (20 eyes)	4	0 20	11	0 12	4	0 01	1	0 10

Comparison with groups of unilateral retinal detachment

Later op	Successful		Unsuccessful	
Extent of detachment	1 2/4		1 2/4	
	Unilateral	Bilateral	Unilateral	Bilateral
n	111	22	[illegible]	11
b pot. mV (mean value)	0 1,	0 12	0 05	0 12
Difference	0 02,		0 010	
Standard error	0 01,		0 01	
t	1 9		2 7,	
P	>0 0,		<0 0,	
Significance	0			

In cases in which other complicating eye diseases are present and detachment is feared to exist the value of the ERG curve is considerable As an example of such a situation we can take cases of chronic uveitis with cataract in which the details of the fundus cannot be seen at ophthalmoscopy If the ERG is extinguished a suspicion of retinal detachment arises and the prospects of improved vision after operation for cataract are presumably exceedingly small

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Extent of detachment

	0–1/4	1/4–2/4	2/4–3/4	3/4–4/4
Bilateral retinal detachment	*n* b pot. mV	*n* b-pot. mV	*n* b pot. mV	*n* b-pot. mV
Later operation successful (40 eyes)	13 0.24	22 0.12	4 0.0[illegible]	1 0.00
Later operation unsuccessful (20 eyes)	4 0.20	11 0.12	4 0.04	1 0.00

Comparison with groups of unilateral retinal detachment

Later op	Successful		Unsuccessful	
Extent of detachment	1/4–2/4		1/4–2/4	
	Unilateral	Bilateral	Unilateral	Bilateral
n	111	22	33	11
b pot. mV (mean value)	0.1[illegible]	0.12	0.08	0.12
Difference	0.029		0.040	
Standard error	0.015		0.017	
t	1.93		2.35	
P	> 0.05		< 0.05	
Significance	0		*	

In cases in which other complicating eye diseases are present, and detachment is feared to exist, the value of the ERG curve is considerable. As an example of such a situation, we can take cases of chronic uveitis with cataract in which the details of the fundus cannot be seen at ophthalmoscopy. If the ERG is extinguished a suspicion of retinal detachment arises and the prospects of improved vision after operation for cataract are presumably exceedingly small.

Two factors appear to be of essential importance in the matter of this confusion concerning the origin of the cysts In part the named authors were not familiar with the normally occurring crypt formations in the conjunctiva and in part the studies have been performed by an ill suited technique as a rule on very small materials In respect to the former factor it has been demonstrated that intraepithelial as well as subepithelial mucous crypts occur in the conjunctiva under normal conditions (*Kessing* 1968 A) and it seems probable that epithelial cysts may develop from these crypts As far as the technique is concerned a whole mount method (*Kessing* 1968 A) must be the only practicable possibility Conventional serial sectioning of a large material is extremely *time consuming* and at the same time it affords little changes of giving a spatial impression of the cysts

The object of the present study was to classify normally occurring epithelial cycts if any on the basis of their origin and to study the relative occurrence and topographic distribution of the individual types as well as variations in their number according to the patient s age

Method and Material

The method used was the previously described whole mount technique (*Kessing* 1968 A) in which whole normal conjunctival sacs are rendered transparent by immersion into a special clearing fluid after modified combined PAS Alcian blue staining This Technique in which the mucosa is not sectioned but left intact stains primarily mucous and serous cells the ordinary epithelial cells staining only very faintly Thus it is easy to locate all cyst formations in a conjunctival sac and morphological as well as quantitative studies may be carried out The various structures of particular interest may be cut out of the whole mount and thereafter sectioned and stained by the usual histological technique For the present study the author used a previously described material of 8 whole conjunctival sacs removed post mortem which had shown no signs of abnormality on inspection or on quantitative studies of intraepithelial neutrophilic leukocytes or subconjunctival lymphocytes (*Kessing* 1968 A) These specimens represent all age groups a few even being from foetuses aged 6 8 months Details of the age distribution have been given in a previous publication *Kessing* 1968 A)

In addition a few of the investigations to be reported below included also 8 biopsies of normal looking conjunctivae (*Kessing* 1968 A) These specimens were processed in the same way

Classification Morphology and Origin

The investigations revealed that intraepithelial as well as subepithelial cysts

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EPITHELIAL CYSTS IN THE CONJUNCTIVA

BY

SVEND VEDEL KESSING

There have been numerous reports on epithelial cysts in the conjunctiva As early as 1904 *Saemisch* in a paper on conjunctival cysts referred to 88 previous cases the first one from 1748

Nevertheless it is usually stated to this very day that in most cases the origin of these cysts is unknown (*Hogan & Zimmerman* 1962 *Duke-Elder* 1965) This is emphasized by the multitude of more or less hypothetical explanations advanced in respect to their origin

It has been stated for instance that epithelial cysts may arise by dilatation of the excretory ducts of accessory *lacrimal glands* secondary formation of lumina in epithelial downgrowths due to inflammation agglutination of mucosal folds in inflammatory conjunctival diseases and by conjunctival injury in the form of implantation cysts (*Saemisch* 1904 *Palich-Szanto* 1956 *Norn* 1959 *Brownell* 1960 *Kiffney* 1962 *Mortada* 1963 *Duke-Elder* 1965 *Babel & Aran a* 1966) In addition to these possibilities it was claimed by *Cirincione* (1904) that the cysts may arise from normally occurring crypts while *Kornerup* (1949) believed that bulbar cycts originated in the normally occurring epithelial relief in the limbal area of the conjunctiva

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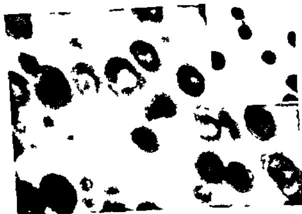
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This work has been supported by grants from the Danish State Research Foundation


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4a


1b

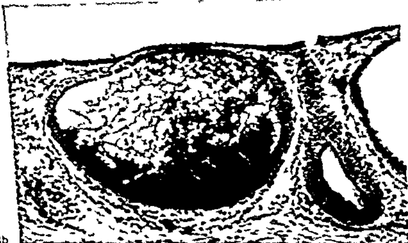

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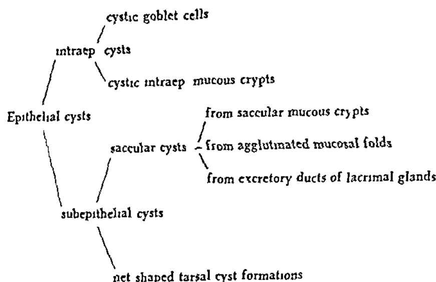
Fig 3

Cystic goblet cells in the bulbar area of a 79 year old woman a Photomicrograph of whole mount (No 55 × 470) (Insert Normal goblet cells in the bulbar area of a 7? year old woman) b Section through one of the cystic goblet cells (Lab No 395/95 Alcian blue PAS × 750)

Fig 4

Subepithelial mucous polycystic formations caused by agglutination of mucosal folds in the lower fornix of a 77 year old woman a Photomicrograph of whole mount (No 79 × 47) b Section through the same cysts with goblet cell secretion in a gel configuration superiorly and amorphous granular masses inferiorly (cf also the text) (Lab No 272/66 Alcian blue PAS × 188)

occur normally in the conjunctiva On the basis of their morphology and origin they were classified as follows



Intraepithelial Cysts

Cystic goblet cells

Fig 1 a presents a photomicrograph of a whole mount showing numerous dilated goblet cells with stagnation of secretion In several respects they differ from normal goblet cells (inserted in Fig 1 a) Partly the stagnated secretion makes them ² 3 times larger than normal conjunctival goblet cells i e 20 40 μ in width and partly they consist of a large homogeneous mass which stains only with PAS but is surrounded by PAS as well as Alcian blue positive material with a normal thready mucus configuration In normal goblet cells all the secretion stains with PAS as well as with Alcian blue (*Kessing* 1968 a) The above mentioned appearances are clearly shown in Fig 1 b which is a photomicrograph of a section through one of the dilated goblet cells This also shows that there is not as normally a goblet cell stoma to the free surface but a continuous layer of flat epithelial cells superficially to the dilated goblet cell Accordingly it must be presumed that the goblet cell cyst is formed because primary epithelial changes *prevent the* formation of the usual stoma so that stagnation of secretion results

Cystic intraepithelial mucous crypts

Fig 2 a which is a photomicrograph of a whole mount, shows among the normal mucous intraepithelial crypts (*Kessing* 1968 A) a few larger dilated crypts

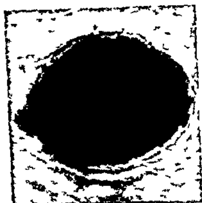
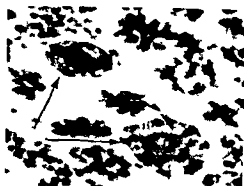


Fig 5
Subepithelial solitary saccular mucous cyst arising from a lacrimal gland primordium in the upper fornix of an 8 month old foetus Photomicrograph of whole mount (No 92 × 188)

tion of microscopic mucosal folds caused by subepithelial accumulation of lymphocytes as there are in Fig 4 a all transitions from very small elongated narrow cysts to larger round ones Fig 4 b shows apart from subepithelial accumulation of lymphocytes that the larger round cysts are formed by dilatation of the small narrow cysts due to accumulation of goblet cell secretion Moreover it is clearly evident from this picture that as in the cysts described above there is both normal PAS positive and Alcian blue positive goblet cell secretion of a typical thready mucous configuration and granular goblet cell secretion which only takes the PAS staining The latter type of secretion is presumably represented by the white granules often seen on biomicroscopy of cyst formations in the inferior fornix

From Fig 5 a + b it is apparent that the polycystic formations reproduced in this figure arise by dilatation of excretory ducts from the accessory lacrimal glands Fig 5 b shows that this dilatation is due to closure of the opening of the excretory duct to the surface resulting in accumulation of tears

While the two types of polycystic formations are easy to distinguish in whole mounts, this may be difficult in sections since due to pressure by the secretion in the cyst the epithelium may be a flattened two layered epithelium in both cases and containing goblet cells in both Serial sectioning however will always – in the latter type of cyst – reveal lacrimal gland tissue in immediate relation to the cyst formation (cf Fig 5 b) and frequently sections from cysts formed by agglutination of mucosal folds will show preserved mucous secretion (cf Fig 4 b) while cysts from lacrimal glands are empty (Fig 5 b)


2a


2b

Fig 2
Cystic intraepithelial mucous crypts on the semilunar fold of an 82 year old woman (arrows) a Photomicrograph of whole mount (No 11 × 188) b Section through a cyst (Lab No 214/66 Alcian blue PAS × 470)

containing granular PAS positive but Alcian blue negative masses as well as smaller quantities of normally PAS as well as Alcian blue positive mucus Fig 2 b presents a section through one of the dilated crypts which is 2 3 times larger than the normal intraepithelial crypts or 100 200 μ It is apparent also from this figure that a flattened layer of cells is present superficially to the crypt without the usual stoma to the surface (*Kessing* 1968 A) As in the case of the goblet cell cyst it must be assumed *therefore that the primary factor in* the cyst formation is an epithelial change preventing the presence of the usual stoma to the surface

Subepithelial Cysts

Saccular cysts

The saccular cysts occur partly as solitary cysts and partly as polycystic for *mations*

Fig 3 is a photomicrograph of a solitary saccular cyst filled with mucus in the superior fornix of an 8 month old foetus Within the same area there are small mucous saccular crypts of the same nature as the small mucous lacrimal gland primordia which occur normally in foetuses children and adults (*Kessing* 1968 A) It is reasonable to assume therefore that the solitary saccular cysts occur because of closure of the named mucous crypts resulting in accumulation of goblet cell secretion

The polycystic formations present themselves partly as shown in Fig 4 a + b and partly as shown in Fig 5 a + b

The cysts illustrated on Fig 4 a + b have presumably formed by agglutina

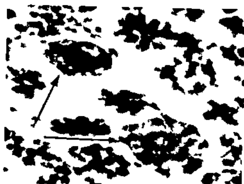


Fig 3
Subepithelial solitary saccular mucous cyst arising from a lacrimal gland primordium in the upper fornix of an 8 month old foetus Photomicrograph of whole mount (No 97 × 139)

tion of microscopic mucosal folds caused by subepithelial accumulation of lymphocytes as there are in Fig 4 a all transitions from very small elongated narrow cysts to larger round ones Fig 4 b shows apart from subepithelial accumulation of lymphocytes that the larger round cysts are formed by dilatation of the small narrow cysts due to accumulation of goblet cell secretion Moreover it is clearly evident from this picture that as in the cysts described above there is both normal PAS positive and Alcian blue positive goblet cell secretion of a typical thready mucous configuration and granular goblet cell secretion which only takes the PAS staining The latter type of secretion is presumably represented by the white granules often seen on biomicroscopy of cyst formations in the inferior fornix

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2a


2b

Fig 2
Cystic intraepithelial mucous crypts on the semilunar fold of an 82 year old woman (arrows) a Photomicrograph of whole mount (No 11, × 188) b Section through a cyst (Lab No 214/66 Alcian blue PAS × 470)

containing granular PAS positive but Alcian blue negative masses as well as smaller quantities of normally PAS- as well as Alcian blue positive mucus Fig 2 b presents a section through one of the dilated crypts which is 2 3 times larger than the normal intraepithelial crypts or 100 200 μ It is apparent also from this figure that a flattened layer of cells is present superficially to the crypt without the usual stoma to the surface (*Kessing* 1968 A) As in the case of the *goblet cell cyst it must be* assumed therefore that the primary factor *in the* cyst formation is an epithelial change preventing the presence of the usual stoma to the surface

Subepithelial Cysts

Saccular cysts

The saccular cysts occur partly as solitary cysts and partly as polycystic formations

Fig 3 is a photomicrograph of a solitary saccular cyst filled with mucus in the superior fornix of an 8 month old foetus Within the same area there are small mucous saccular crypts of the same nature as the small mucous lacrimal gland primordia which occur normally in foetuses children and adults (*Kessing* 1968 A) It is reasonable to assume therefore that the solitary saccular cysts occur because of closure of the named mucous crypts resulting in accumulation of goblet cell secretion

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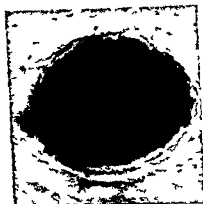


Fig 5

Sul epithelial solitary saccular mucous cyst arising from a lacrimal gland primordium in the upper fornix of an 8 month old foetus Photomicrograph of whole mount (No ?? × 183)

tion of microscopic mucosal folds caused by subepithelial accumulation of lymphocytes as there are in Fig 4 a all transitions from very small elongated narrow cysts to larger round ones Fig 4 b shows apart from subepithelial accumulation of lymphocytes that the larger round cysts are formed by dilatation of the small narrow cysts due to accumulation of goblet cell secretion Moreover it is clearly evident from this picture that as in the cysts described above there is both normal PAS positive and Alcian blue positive goblet cell secretion of a typical thready mucous configuration and granular goblet cell secretion which only takes the PAS staining The latter type of secretion is presumably represented by the white granules often seen on biomicroscopy of cyst formations in the inferior fornix

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Fig 5

Subepithelial polycystic *formations due to accumulation of tears in the excretory* duct of an accessory lacrimal gland in the upper fornix of a 49 year old woman a Photo micrograph of whole mount with lacrimal gland tissue superiorly (No 54 × 15) b Section through the cysts showing closure of the opening of the extretory duct to the surface (arrow) (Lab No 3/6 65 haem eosin × 75)

Net shaped cyst formations

Fig 6 illustrates net shaped cyst formations from the upper tarsal area These cysts arise from closure of the net shaped mucous crypt systems which occur normally in the tarsal areas (*Kessing* 1968 A) The cysts are filled with accu mulated goblet cell secretion consisting predominantly like the mucous cysts described above on mucous which takes only PAS *staining*



Fig 6

Subepithelial net shaped mucous cyst formations in the upper tarsal area of a 65 year old man Photomicrograph of whole mount (No 24 X 188)

Topography and Occurrence

Within the normal material studied cystic goblet cells occurred almost exclusively in the bulbar conjunctiva and primarily in the upper temporal quadrant In this area cystic goblet cells with accumulation of secretion were found in 4% of all 78 whole mounts while in the upper nasal quadrant they were present in only 11% and in the lower temporal and lower nasal quadrants in only 1% and 2% respectively

Cystic intraepithelial mucous crypts occur first and fore most on the semilunar fold (% of the whole mounts showing crypts with stagnated mucin at this site They were found also in 34% in the lower fornix in 15% nasally on the bulbar conjunctiva and in 6% in the upper fornix

Saccular mucous cysts i e the solitary saccular cysts as well as polycystic formations from agglutinated mucosal folds were found in 53% of all the specimens in the lower fornix and in 50% in the upper fornix On the other hand polycystic formations derived from the excretory ducts of the lacrimal glands were present in only 17% of the whole mounts primarily in the upper fornix This accords with the finding that this is by far the most common site of accessory lacrimal glands (*Kessing* 1968 B) The excretory ducts from the lacrimal gland were found to be slightly dilated in a few cases but the present material did not include examples of true cysts arising from these structures





Fig 5

Subepithelial polycystic formations due to accumulation of tears in the excretory duct of an accessory lacrimal gland in the upper fornix of a 79 year old woman a Photo micrograph of whole mount with lacrimal gland tissue superiorly (No 54 X 75) b Section through the cysts showing closure of the opening of the extretory duct to the surface (arrow) (Lab No 376 65 haem eosin X 75)

Net shaped cyst formations

Fig 6 illustrates net shaped cyst formations from the upper tarsal area These cysts arise from closure of the net shaped mucous crypt systems which occur normally in the tarsal areas (*Kessing* 1968 A) The cysts are filled with accu mulated goblet cell secretion consisting predominantly like the mucous cysts described above on mucous which takes only PAS staining



Fig 6

Subepithelial net shaped mucous cyst formations in the upper tarsal area of a 65 year old man Photomicrograph of whole mount (No 24 × 188)

Topography and Occurrence

Within the normal material studied cystic goblet cells occurred almost exclusively in the bulbar conjunctiva and primarily in the upper temporal quadrant In this area cystic goblet cells with accumulation of secretion were found in 94 % of all 78 whole mounts while in the upper nasal quadrant they were present in only 11 % and in the lower temporal and lower nasal quadrants in only 1 % and 2 % respectively

Cystic intraepithelial mucous crypts occur first and fore most on the semi lunar fold 76 % of the whole mounts showing crypts with stagnated mucin at this site They were found also in 34 % in the lower fornix in 15 % nasally on the bulbar conjunctiva and in 6 % in the upper fornix

Saccular mucous cysts i e the solitary saccular cysts as well as polycystic *formations from agglutinated mucosal folds* were found in 58 % of all the specimens in the lower fornix and in 50 % in the upper fornix On the other hand polycystic formations derived from the excretory ducts of the lacrimal glands were present in only 17 % of the whole mounts primarily in the upper fornix This accords with the finding that this is by far the most common site of accessory lacrimal glands (*Kessing* 1968 B) The excretory ducts from the lacrimal gland were found to be slightly dilated in a few cases but the present material did not include examples of true cysts arising from these structures



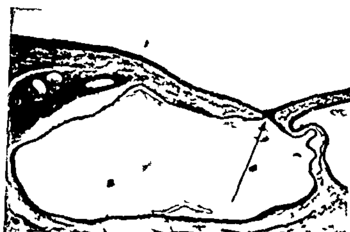


Fig 5

Subepithelial polycystic *formations due to accumulation of tears in the excretory duct* of an accessory lacrimal gland in the upper fornix of a 79 year old woman a Photo micrograph of whole mount with lacrimal gland tissue superiorly (No 54 × 75) b Section through the *cysts showing closure of the opening of the extretory duct* to the surface (arrow) (Lab No 376/65 haem eosin × 75)

Net shaped cyst formations

Fig 6 illustrates net shaped cyst formations from the upper tarsal area These cysts arise from closure of the net shaped mucous crypt systems which occur normally in the tarsal areas *(Kessing 1968 A)* The cysts are filled with accu mulated goblet cell secretion consisting predominantly *like the mucous cysts described above on mucous which takes only PAS staining*



Fig 6
Subepithelial net shaped mucous cyst formations in the upper tarsal area of a 65 year old man Photomicrograph of whole mount (No 94 × 189)

Topography and Occurrence

Within the normal material studied cystic goblet cells occurred almost exclusively in the bulbar conjunctiva and primarily in the upper temporal quadrant In this area cystic goblet cells with accumulation of secretion were found in 94 % of all 78 whole mounts while in the upper nasal quadrant they were present in only 11 % and in the lower temporal and lower nasal quadrants in only 1 % and 2 % respectively

Cystic intraepithelial mucous crypts occur first and fore most on the semi lunar fold 6 % of the whole mounts showing crypts with stagnated mucin at this site They were found also in 34 % in the lower fornix in 15 % nasally on the bulbar conjunctiva and in 6 % in the upper fornix

Saccular mucous cysts i e the solitary saccular cysts as well as polycystic formations from agglutinated mucosal folds were found in 53 % of all the specimens in the lower fornix and in 50 % in the upper fornix On the other hand polycystic formations derived from the excretory ducts of the lacrimal glands were present in only 17 % of the whole mounts primarily in the upper fornix This accords with the finding that this is by far the most common site of accessory lacrimal glands (*Kessing* 1968 B) The excretory ducts from the lacrimal gland were found to be slightly dilated in a few cases but the present material did not include examples of true cysts arising from these structures

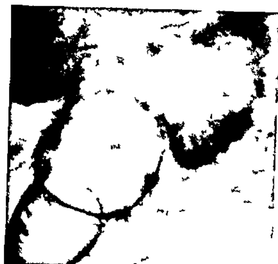




Fig 5

Subepithelial polycystic formations due to accumulation of tears in the excretory duct of an accessory lacrimal gland in the upper fornix of a 79 year old woman a Photo micrograph of whole mount with lacrimal gland tissue superiorly (No 54 X 45) b Section through the cysts showing closure of the opening of the extretory duct to the surface (arrow) (Lab No 376/65 haem eosin X 75)

Net shaped cyst formations

Fig 6 illustrates net shaped cyst formations from the upper tarsal area These cysts arise from closure of the net shaped mucous crypt systems which occur normally in the tarsal areas (*Kessing* 1968 A) The cysts are filled with accumulated goblet cell secretion consisting predominantly like the mucous cysts described above on mucous which takes only PAS staining



Fig 6

Subepithelial net shaped mucous cyst formations in the upper tarsal area of a 65 year old man Photomicrograph of whole mount (No 74 × 188)

Topography and Occurrence

Within the normal material studied cystic goblet cells occurred almost exclusively in the bulbar conjunctiva and primarily in the upper temporal quadrant In this area cystic goblet cells with accumulation of secretion were found in 34 % of all 78 whole mounts while in the upper nasal quadrant they were present in only 11 % and in the lower temporal and lower nasal quadrants in only 1 % and 2 % respectively

Cystic intraepithelial mucous crypts occur first and fore most on the semi lunar fold 76 % of the whole mounts showing crypts with stagnated mucin at this site They were found also in 34 % in the lower fornix in 15 % nasally on the bulbar conjunctiva and in 6 % in the upper fornix

Saccular mucous cysts i e the solitary saccular cysts as well as polycystic formations from agglutinated mucosal folds were found in 53 % of all the specimens in the lower fornix and in 50 % in the upper fornix On the other hand polycystic formations derived from the excretory ducts of the lacrimal glands were present in only 17 % of the whole mounts primarily in the upper fornix This accords with the finding that this is by far the most common site of accessory lacrimal glands (*Kessing* 1968 B) The excretory ducts from the lacrimal gland were found to be slightly dilated in a few cases but the present material did not include examples of true cysts arising from these structures





Fig 5
Subepithelial polycystic formations due to accumulation of tears in the excretory duct of an accessory lacrimal gland *in the upper fornix of a 79 year old woman* a Photo micrograph of whole mount with lacrimal gland tissue superiorly *(No 54 × 15)* b Section through the cysts showing closure of the opening of the extretory duct to the surface *(arrow)* (Lab *No 376/65 haem eosin × 75)*

Net shaped cyst formations

Fig 6 illustrates net shaped cyst formations from the upper tarsal area These cysts arise from closure of the net shaped mucous crypt systems which occur normally in the tarsal areas *(Kessing* 1968 A) The cysts are filled with accumulated goblet cell secretion consisting predominantly like the mucous cysts described above on mucous which takes only *PAS staining*

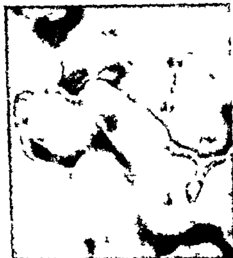


Fig 6
Subepithelial net shaped mucous cyst formations in the upper tarsal area of a 62 year old man Photomicrograph of whole mount (No 24 × 188)

Topography and Occurrence

Within the normal material studied cystic goblet cells occurred almost exclusively in the bulbar conjunctiva and primarily in the upper temporal quadrant In this area cystic goblet cells with accumulation of secretion were found in 74% of all 78 whole mounts while in the upper nasal quadrant they were present in only 11% and in the lower temporal and lower nasal quadrants in only 1% and 9% respectively

Cystic intraepithelial mucous crypts occur first and fore most on the semilunar fold 76% of the whole mounts showing crypts with stagnated mucin at this site They were found also in 34% in the lower fornix in 15% nasally on the bulbar conjunctiva and in 6% in the upper fornix

Saccular mucous cysts i e the solitary saccular cysts as well as polycystic formations from agglutinated mucosal folds were found in 58% of all the specimens in the lower fornix and in 50% in the upper fornix On the other hand polycystic formations derived from the excretory ducts of the lacrimal glands were present in only 17% of the whole mounts primarily in the upper fornix This accords with the finding that this is by far the most common site of accessory lacrimal glands (*Kessing* 1968 B) The excretory ducts from the lacrimal gland were found to be slightly dilated in a few cases but the present material did not include examples of true cysts arising from these structures

Lastly, the upper tarsal area showed net shaped cyst formations in 45 % of the whole mounts the lower tarsal area in 38 %

Age Variations in the Number of Epithelial Cysts

To gain an impression of age variations in the number of epithelial cysts due to stagnation of mucus in epithelial mucous structures it was attempted to assess the stagnation of mucus in these structures in all the whole mounts A rough division into four grades was used

Grade 0 No stagnation of mucus
Grade 1 Stagnation in a few of the studied structures
Grade 2 Stagnation in a number of the studied structures
Grade 3 Stagnation in most of the studied structures

In studying the stagnation of mucin in goblet cells the 78 whole conjunctival sacs removed post mortem and the biopsies were divided into 8 age groups Two of these age groups represent foetal specimens and specimens from the first year of life while the others represent 15 year intervals up to the age of 90 years

The age variation found by studying the 4 quadrants of the bulbar conjunctiva in which the cystic goblet cells mostly occur is shown in Fig 7 The figure shows the relation between the average grading and the average age in the different age groups It is apparent that cystic goblet cells occur with increasing frequency from the age of approx 20 and especially in the upper temporal quadrant Within this quadrant the age group 31 45 years showed cystic goblet cells in 16 % of all the specimens the age group 46 60 years in 28 % the age group 61 75 years in 50 % and the age group 76 90 years in 73 % of all the specimens

Fig 8 gives the results of a similar grading of mucus stagnation in the intra epithelial mucous crypts of the 78 post mortem whole specimens It may be seen that cyst formation in these structures also increases appreciably with advancing age and that the cysts occur particularly on the semilunar fold where they were observed in all age groups

The grading of mucus stagnation in the mucous saccular structures comprised solitary cysts as well as mucous polycystic formations In this type too an increased stagnation occurred with advancing age (Fig 9) Stagnation of mucus increases quite particularly in the oldest age group especially in the lower fornix Strangely enough the group of foetal specimens also showed some stagnation of mucus in solitary saccular structures Epithelial polycystic formations from the excretory ducts of accessory lacrimal glands also occurred pre

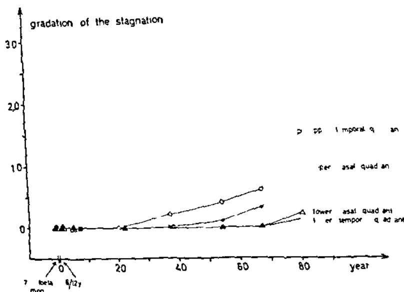


Fig 7
Age variations in the degree of stagnation of secretion in goblet cells on the bulbar conjunctiva (cf also the text)

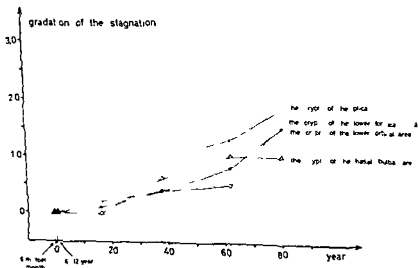


Fig 8
Age variations in the degree of stagnation of secretion in intraepithelial mucous crypts (cf also the text)

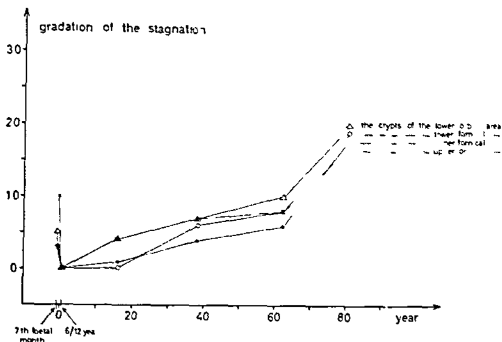


Fig 9
Age variations in the degree of stagnation of secretion in mucous saccular structures (cf also the text)

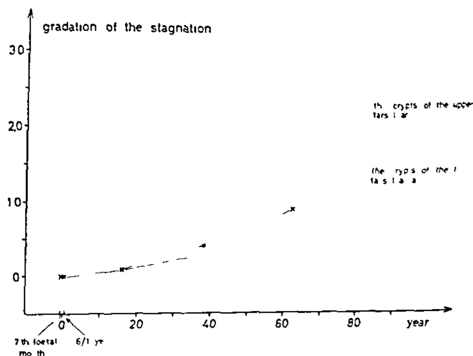


Fig 10
Age variations in the degree of stagnation of secretion in mucous net shaped crypt formations (cf also the text)

dominantly in elderly persons The average age of the group of whole mounts showing these structures was 63 years while that of all specimens without these structures was only 41 years

Fig 10 lastly shows the degree of mucus stagnation in epithelial net shaped structures Just like the other structures these too showed stagnation to be most common in the oldest age group and to occur especially in the upper tarsal area

Discussion and Conclusion

The author s studies have demonstrated that epithelial cysts occur normally in the conjunctiva and that they are due primarily to stagnation of mucus in the normally occurring mucous gland system and in small epithelial pouches formed by the agglutination of microscopic mucosal folds formed by irregular elevation of the epithelial surface due to subconjunctival accumulation of lym phocytes More rarely the cysts have proved to be derived from dilated excre tory ducts of the accessory lacrimal glands

In all cases the cause of the cyst formation seems to be a tendency to agglu tination of the surface epithelium increasing with age This tendency entails closure of all openings in the mucosal surface Possibly it represents age con ditioned atrophy of the conjunctival mucosa

It has been demonstrated also that the cysts contain neutral as well as acid mucopolysaccharides except for those which develop from the serous gland system Since this has been found also for cystic goblet cells both types of mucopolysaccharide must be secretion from goblet cells although normal con junctival goblet cells contain only acid mucopolysaccharides (*Kessing* 1967) At the same time it was observed that the acid mucopolysaccharide in the cysts is precipitated in the usual thready gel configuration while the neutral mucopo lysaccharide is precipitated in amorphous granular masses as seen in the pre cipitation of a sol

Staining the mucous thread in the inferior fornix of the conjunctival sac with toluidine blue *Norn* (1968) found small areas of the thread to stain orthochro matically while the greater part stained metachromatically The orthochroma sia occurred mainly in acute conjunctivitis By histochemical studies of intesti nal goblet cells in human foetuses *Zacchea* & *Vitale* (1958) found int al that immature goblet cells are orthochromatic while fully developed ones show metachromasia when stained with toluidine blue These authors concluded that immature secretion is neutral while mature secretion is acid

Thus the increased tendency to orthochromasia in acute conjunctivitis (*Norn* 1968) is possibly due to increased secretory activity in the goblet cells which give off immature orthochromatic secretion This cannot however explain the

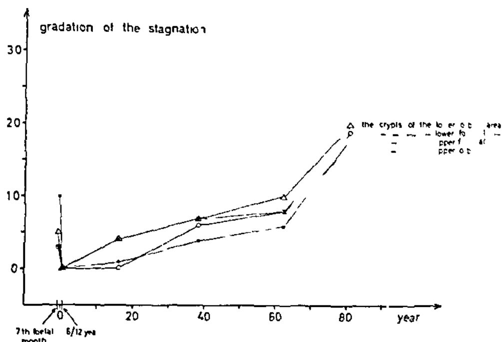


Fig 9
Age variations in the degree of stagnation of secretion in mucous saccular structures (cf also the text)

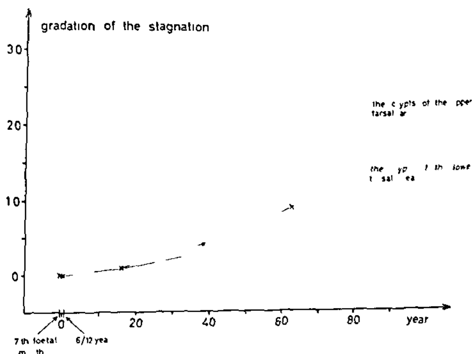


Fig 10
Age variations in the degree of stagnation of secretion in mucous net shaped crypt formations (cf also the text)

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Summary

By the aid of a special whole mount technique the author studied conjunctival epithelial cysts in 78 whole normal conjunctival sacs removed post mortem and 73 biopsies Six different types of epithelial cysts were found The most common ones are formed by stagnation of mucus in the mucous gland system and in small pouches of conjunctival mucosa caused by agglutination of mucosal folds Less commonly the epithelial cysts arise due to accumulation of tears in the excretory ducts of the accessory lacrimal glands The investigations included also topographical studies and studies on age variations in the number of cysts

Lastly it was observed that all cysts with stagnated mucus contain 2 types of goblet cell secretion In part normal mucin of a gel configuration consisting of acid mucopolysaccharides and in part neutral mucopolysaccharides precipitated in amorphous granular masses On the basis of this finding the author advances the hypothesis that by splitting off of acid groups the goblet cell secretion may be converted from gel to sol

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Fig 1
Appear nce of cross country skier immediately after finishing the course

and no snow falling The race track was 15 km and the average time for the course was 50 minutes

Within 30 minutes of passing the finishing line 29 skiers were examined (fig 1) This comprised the majority of the participants the few who abstained were foreigners who obviously thought the examination was a national project

A history was first taken Then the visual acuity was tested using a Snellen chart at 5 meters Inspection of the corneae followed after instillation of one drop Rose Bengal/fluorescein (*Norn* 1964) This was done with a Haag Streit 900 slit lamp using 25 × magnification

Results

History 13 skiers had previously experienced smarting and blurred vision when competing at low temperatures 5 skiers had at some time been compelled to discontinue a race for the same reasons

Vision In 3 skiers the visual acuity was reduced to 5/10 in one or both eyes

Inspection 26 skiers had epithelial damage shown by punctate red staining after instillation of Rose Bengal/fluorescein The stain was only seen in the lower third of the cornea with a fairly sharp convex border toward normal epithelium (fig 2) Green staining was not seen

Three skiers with dense staining also had epithelial bedewing when ex

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University of Oslo Norway
(Head Professor dr med Jan Ytteborg)

COLD INJURY TO CORNEAL EPITHELIUM

A cause of blurred vision in cross-country skiers

BY

ALBERT KOLSTAD and ROALD OPSAHL JR

The eye is the only part of the body surface which cannot be efficiently protected against heat loss by use of clothing In spite of this there are surprisingly few reports of superficial eye injury caused by low ambient temperatures

The few cases reported have dealt with persons concurrently exposed to cold and wind without having been protected by goggles or wind screens Aviators are in the majority (*Colombo* 1921 *Sedan* 1947) although the reports also include a cyclist (*Dubois de Lavigerie* 1895) an ice skater (*Freytag* 1916) and ethnic groups living in Arctic climates (*Freedman* 1965)

It has been brought to our attention that cross country skiers develop blurred vision when competing at very low temperatures A search of the medical literature has thrown no light on this problem It was therefore decided to see if a clinical examination of the skiers made at the place of competition would produce any information

Material and methods

In January 1968 the main body of cross country skiers were competing at the Monolith ski track in Oslo The weather was overcast −16 C with no wind



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the extreme state of visual attention paid to the track although this would probably only be a contributary cause

The epithelial damage is probably explained both by the exposure to cold and wind and by the evaporation and disruption of the tear film The damage is transitory and will usually heal completely in 24 hours

A solution acceptable to the afflicted skiers would have to be directed toward protection of the eyelid and the cornea Use of protective goggles is impractical since these would fog and ultimately become encrusted with ice Suitable head gear might prove a solution possibly combined with the use of contact lenses

Summary

29 cross country skiers competing in −16° C cold were examined for corneal pathology immediately after finishing the course 26 had epithelial staining in lower third of corneae 3 had epithelial bedewing with a decrease in visual acuity Complete healing took place within 24 hours

The epithelial damage is probably caused by incomplete *closure of the* eyelids

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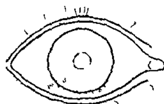


Fig 2
Distribution of punctate epithelial staining with Rose Bengal / *fluorescein*

amined by retro illumination These were the same who had reduced visual acuity mentioned above One skier who wore contact lenses for optical reasons had no staining of the cornea

Discussion

The frequency of positive history indicates a common cause It is noted that only three skiers had reduced vision in the present investigation This is probably explained by the length of the track being only 15 km Most of the skiers claimed that eye problems seldom occured in such a short event They all agreed upon the low air temperature as the main cause, since the problem is never encountered later in the season when the temperature is higher This also excludes ultraviolet radiation as a likely factor

Wind pressure caused by the speed of the skier is certainly of importance In a cross country race the average speed of the skier is close to 20 km/h for a distance which varies between 15 and 50 km In downhill runs the speed may be at least twice as much

The finding of degenerate epithelium in the lower third of the cornea bordered by a convex line toward normal epithelium indicates insufficient protection by the lid Similar distribution of degenerate epithelium has been described in persons sleeping with half open eyes (*Fuchs* 1948) and in des sication keratitis due to extreme fatigue states (*Ayoub* 1944) The same location of epithelial damage is well known in keratitis e lagophthalmo

The open question is thus why the eyelids do not close shut under these extremes of temperature and energy expenditure The lack of subcutaneous fat in the skin of the eye lid as well as its unprotected position would probably explain a drop in tissue temperature where muscle contraction would be seriously impaired This is supported by the observation of a decreasing blink rate in one of the skiers during the race Another explanation may be

the extreme state of visual attention paid to the track although this would probably only be a contributary cause

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ON TIME SERIES ANALYSIS OF VISUAL ACUITY A STATISTICAL MODEL

BY

C E T KRAKAU M D

In two investigations in 1946 Barany (1 2) treated inter alia the variability of visual acuity Barany who used the method of constant stimuli to determine acuity stresses that "a person s visual acuity cannot be characterized by only one figure at least two are required the mean visual acuity around which the population of instantaneous visual acuities are distributed with a dispersion In the following it will be demonstrated that a reasonably complete description of visual acuity demands even more statistical parameters

1 Instantaneous visual acuity as a stochastic process

The assumption that there exists a well defined *instantaneous visual acuity* might be interpreted as follows At any instant the existence of a most difficult test object (such as a Landolt ring) is presumed which is correctly interpreted – like all easier objects whereas the next infinitesimally more difficult one *is* not correctly perceived The limiting object size – which defines instantaneous visual acuity – *is supposed to* vary according to some function $x(t)$ where $x(t)$ is a realization of a stochastic process $\xi(t)$ The properties of this process are of fundamental importance to any testing of acuity

1 1 Marginal distributions

For any t and measure of difficulty x of the test object we define

$$F_t(x) = P\{\xi(t) \geq x\} \qquad (1)$$

Thus $F_t(x)$ is the marginal distribution function of $\xi(t)$ at time t (The expression marginal distribution function is used here in a somewhat unorthodox sense) We also interpret $F_t(x)$ as the probability that at time t an object of difficulty x is correctly interpreted It is a decreasing function of x – continuous or not – which is zero if x is small enough and unity if x is large enough If $F_t(x)$ is the same for all t the marginal distributions are called stationary

1.2 Independence

Let t = 1 2 3 be a sequence of time points when the trials are performed Under the hypothesis of indepence the random variables $\xi(1)$ $\xi(2)$ are independent Then the marginal distributions completely describe the behaviour of the process at these points

The hypothesis of independence can be criticized for several reasons Slow effects of tiring or of training fluctuations in attention variations in the neuronal excitability etcetera might alter the statistical parameters of the process during an experiment If the time interval between successive trials is short enough it seems natural to assume that the acuities observed at these instants are correlated However if the interval is considerable the hypothesis might be at least approximatively true Evidently it is of great interest to test the hypothesis of independence and we shall later outline how such a test might be performed

1.3 Stationarity of the process

A *time series* is said to be *stationary* in the wide sense (or in Khinchin s sense)

if its mean value $E\,\xi(t) = \int_{-\infty}^{\infty} x\,dF_t(x)$ (2)

is a constant and if its correlation function $E\{\xi(s)\,\xi(t)\} = B(t\ s)$ (3)

depends only on $t - s = \tau$ When the trials are independent then $B(\tau) = 0$ for all $\tau \geq 1$

2. Procedure using constant stimuli

A procedure using constant stimuli – *which* does not directly aim at the instantaneous acuity – is based on the following idea For any *experimentee* there are objects which on every *trial* are interpreted correctly *i e* the probability that they are seen is unity On the other hand the *objects* can be made so difficult to discern that their interpretation is merely *guesswork* Between these two

extremes there are objects which are not always correctly interpreted though more often so than on pure guessing These facts are perfectly in accordance with the properties of the "marginal distributions" $F_t(x)$ described in 1 1

Now let E_1 E_2 be a set of test objects of increasing difficulty For brevity we also use the same symbols for the measures of difficulty of the objects Let $p_i(t)$ be the probability that E_i is correctly interpreted at time t From (1) we see that $p_i(t) = F_t(E_i)$ Evidently p_i is a decreasing sequence

If the stationarity assumption described in 1 1 is true $p_i(t)$ is independent of t and is written simply as p_i

Let us suppose that a series of trials is performed at times $t = 1\ 2\ 3$ where the experimentee is shown a sequence of objects E_{i1} E_{i2} chosen before the experiment The outcome of the trials largely depends on the properties of the process $\xi(t)$ described earlier

First suppose that the hypothesis of independence and stationarity of the marginal distribution are both true Then the visual testing can be considered as a number of replicated independent trials with given success probabilities $\{P_i\}$ An estimate p_i of p_i might then be obtained by showing the object E_i a number of times and taking p_i^* as the ratio of the number of correct interpretation and the total number of trials

Secondly suppose that only the hypothesis of $\xi(t)$ being a stationary process is true Then the results of the trials are dependent and the model of replicated trials is no longer true

3 A special test procedure

3 1 General description

In the rest of the paper we consider the following test procedure If the experimentee interprets the object E_i correctly, he is immediately shown the next difficult E_{i+1} If he interprets E_i erroneously he is shown the next simple object E_{i-1} When the starting point is given this procedure is well defined and the sequence of states visited say E_{i1} E_{i2} E_{i3} is a realization of a stochastic process $\eta(t)$ $t = 1\ 2$

Since all objects over a certain size say E_h are interpreted correctly with probability unity a process which starts at an object easier than E_h rapidly moves to E_h and more difficult objects and does not reappear on objects easier than E_h Since the number of objects is limited there is another object F_m which is the most difficult one Thus the possible states of the process can conveniently be denoted E_1 E E_m

The properties of $\eta(t)$ are determined by those of the process $\xi(t)$ discussed above In this section we shall assume that $\eta(t)$ is a stationary Markov chain (We will discuss in the next section the conditions which then have to be imposed on $\xi(t)$)

Let the probalıty of a transition from E to E $_{+1}$ be denoted by $p_{i\ +1}$ and from E_i to E $_{-1}$ by $p_{i\ -1}$. We observe that p $_{+1}$ is then the probability that E_i is interpreted correctly. The transition matrix P of the chain can then be written as follows

	E_1	E_2	E_3		E_{m-1}	E_m
E_1		1				
E	p_{21}		$p_{\ 3}$			
E_3		p_3		p_{34}		
$E_{m\ 1}$				$p_{m-1\ m-}$		$p_{m-1\ m}$
E_m					$p_{m\ m-1}$	$p_{m\ m}$

(4)

If it is presumed that the transition probabilities are constant, this matrix together with the starting point of the process defines a so called stationary Markov chain. We will later discuss whether this assumption is warranted. In the present case the process cannot reach objects easier than E_1 or more difficult ones than E_m and it can be considered as a finite random walk with barriers at the states E_1 and E_m.

A process which may be called y (t) starting in some state E_i will after a number of steps N be in the state E_k with the probability $p_k^{(N)}$. Since the process is stationary irreducible and non periodic (Feller (3) p 349 ff) we have

$$\lim_{N \to \infty} p_k^{(N)} = \pi_k > 0 \quad \Sigma \pi = 1 \tag{5}$$

The set $\{\pi\}$ defines a stationary distribution which satisfies a system of linear equations

$$\pi = \pi_{i\ 1} p_{\ \ 1} + \pi_{+1} p_{+1} \quad \pi_m = \pi_{m\ 1} p_{m-1\ m} + \pi_m p_{mm} \quad (i < m) \tag{6}$$

In practice the probability sets are estimated by a limited number of transitions and visits on different states. Let n_{i+1} be the number of transitions during an experiment of a total of M trials from the state E_i to E $_{+1}$ and n the number of visits to the state E. Then we have the following relations

$$p^*_{\ \ +1} = \frac{n_{\ \ 1}}{n_{i\ \ 1} + n_{\ +1}} \quad n = n_{\ +1} + n_{\ -1} \quad \Sigma n = M \tag{7}$$

If the process starts and ends on the same state we have

$$n_{\ \ 1} = n_{\ +1} \quad \text{otherwise} \ /n_{+1} - n_{\ +1}/ \leq 1 \tag{8}$$

a difference which can be neglected when the number of transitions is large. We can easily show that the corresponding estimate of π

$$\pi = \frac{n_{\ +1} + n_{\ \ 1}}{\Sigma n} = \frac{n_i}{M} \tag{9}$$

satisfies the system (6)

extremes there are objects which are not always correctly interpreted though more often so than on pure guessing These facts are perfectly in accordance with the properties of the marginal distributions $F_t(x)$ described in 1 1

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If the stationarity assumption described in 1 1 is true $p_i(t)$ is independent of t and is written simply as p_i

Let us suppose that a series of trials is performed at times t = 1 2 3 where the experimentee is shown a sequence of objects E_{i1} E_i chosen before the experiment The outcome of the trials largely depends on the properties of the process $\xi(t)$ described earlier

First suppose that the hypothesis of independence and stationarity of the marginal distribution are both true Then the visual testing can be considered as a number of replicated independent trials with given success probabilities $\{P_i\}$ An estimate p_i^* of p_i might then be obtained by showing the object E_i a number of times and taking p_i as the ratio of the number of correct interpretation and the total number of trials

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3 A special test procedure

3 1 *General description*

In the rest of the paper we consider the following test procedure If the experimentee interprets the object E_i correctly he is immediately shown the next difficult E_{+1} If he interprets E_i erroneously he is shown the next simple object E_{i-1} When the starting point is given this procedure is well defined and the sequence of states visited say E_{i1} E_{i2} E_{i3} is a realization of a stochastic process $\eta(t)$ t = 1 2

Since all objects over a certain size say E_h are interpreted correctly with probability unity a process which starts at an object easier than E_h rapidly moves to E_h and more difficult objects and does not reappear on objects easier than E_h Since the number of objects is limited there is another object E_m which is the most difficult one Thus the possible states of the process can conveniently be denoted E_1 E_2 E_m

The properties of $\eta(t)$ are determined by those of the process $\xi(t)$ discussed above In this section we shall assume that $\eta(t)$ is a stationary Markov chain (We will discuss in the next section the conditions which then have to be imposed on $\xi(t)$)

With a suitably chosen set of states we may let the value of the function y (t) be the number of the states visited The correlation function for the Markov process is then given by

$$B^{(1)}(N) = \Sigma_i \pi_i \quad i \quad \Sigma_j p_{ij}^{(N)} \quad j \tag{12}$$

However the calculation of B (N) in this manner is elaborate and an approximative method may be tried The correlation function for a normal Markov chain is of the form (Yaglom (5) p 112)

$$R^{(\,)}(\tau) = C a^{\tau} \quad C > 0 \quad a < 1 \quad \tau = 0 \ 1 \ 2 \tag{13}$$

The actual process is not normal – it takes for instance only discrete values – but it may sometimes be of practical interest to calculate the correlation function as if the process were normal Hence

$$R^{(2)}(0) = C \quad R(1)/R(O) = a \tag{14}$$

The constant a can be determined from the sets $\{p_j\}$ and $\{\pi\}$

$$B^{*}(1) = \Sigma \pi_i \quad i \, [p^{*} \quad _{+1} \quad (i+1) + p^{*} \quad _{-1} \quad (i-1]$$

$$= \frac{1}{M} \Sigma \quad i \, [n \quad _{+1} \quad (i+1) + n \quad _{1} \quad (i-1)] = \frac{1}{M} \Sigma n \quad i \quad - \tfrac{1}{2}$$

$$= B^{*}(0) - \tfrac{1}{2}$$

where n_j and n_j are presumed to be equal The centered function R is obtained by subtracting Mm^2 (m = the mean of y) from B The function $R^{(2)}(\tau)$ of eq 13 can then be drawn

The comparison between the correlation function estimated according to eq (11) and the approximative one (eq 13) representing a stationary Markov process gives some idea of the dependence between the trials of the process y (t) Some kind of criterion has to be constructed by means of which the significance of a deviation between the two functions can be tested Further the conditions under which the use of the approximative function (13) instead of (12) is justified demand some study

The conclusions which may be drawn from the correlation properties of y (t) concerning those of ² (t) have a bearing also on the stationarity of the process (eq 3) Also for the stationarity condition eq 2 we may rely on the process y (t) The stationarity criteria needed will have to be constructed with due reference to the number of trials possible in practice and other experiences of the behaviour of the function y (t)

An automatic instrument which records the series y (t) has been constructed (6) It is connected to a tape perforator and the statistical parameters are obtained directly from a computor In (6) an example of the function $R^{*}(\tau)$ (normalized by division by R (o)) and R( ) calculated from a recording of the visual acuity is shown

The stationary probabilities $\{\pi_i\}$ can be given a different interpretation than the one quoted above The sum $\sum_{i+1}^{m} \pi_k$ can be taken as an estimate of the probability of finding the process η (t) above the state E_i

3 2 The relation between the processes ξ (t) and η (t)

The relations between the fundamental process ξ (t) describing the variations of visual acuity and the process η (t) generated by the testing procedure defined in the previous section may be treated as follows

In the general case any transition at time t, say from E_i to E_{i+1} is dependent not only on ξ (t) but also on the acuities at earlier times ξ (t — 1), ξ (t — 2) *However in the particular case that the hypothesis of independence is true this transition is seen to depend only on ξ (t) In fact the probability of a transition* is then equal to

$$\Gamma_t (E_i) = P (\xi (t) \geq E_i) = p_{i, i+1}(t) \tag{10}$$

When $\Gamma_t (E_i)$ is stationary (1 1) the transition $E_i \rightarrow E_{i+1}$ depends only on the last state E_i Hence, if the fundamental process ξ (t) is stationary and independent the process generated by the testing procedure η (t) is a stationary Markov chain and the theory outlined in the previous section can be applied to the testing procedure

3 3 An approach to the testing of independence of trials

Obviously the hypothesis to be tested is in the first place whether the process y (t) – a realization of η (t) – is a stationary Markov chain (the process ξ (t) made up by independent variables) or not In the latter case we are interested in estimating the degree of dependence The following approach to this problem is a working hypothesis the adequacy of which remains to be proved

The *correlation function for the process* y (t) can be estimated by the formula

$$B (\tau) = \lim_{N \to \infty} \frac{1}{N} y (t) y (s) \quad \tau = t - s \quad \tau = 0 \; 1 \; 2 \tag{11}$$

(if the mean of y is zero we call the *correlation function* *centered* and use the notation R (τ))

For a *stationary* Markov chain the correlation function can also be calculated from $\{p_{ij}\}$ and $\{\pi_i\}$ The probability of a *transition from* the i th to the j th state in N steps $p_{ij}^{(N)}$ is obtained from the one step transition matrix P (4) From the Chapman Kolmogorov equation can be derived (cf Parzen (4) p 195) that $P^N = P (N)$ where P^N stands for successive matrix multiplications of N matrices P and P (N) is the N step transitions matrix $\{p_{ij}^{(N)}\}$

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HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the University Eye Clinic Rigshospitalet
Blegdamsvej Copenhagen Denmark
(Heads Professor H Ehlers M D and J Edmund M D)

PHOTOCOAGULATION IN PROLIFERATIVE DIABETIC RETINOPATHY*)

A preliminary report

BY

HANS-WALTHER LARSEN

During the last few years quite favorable results of photocoagulation have been reported in proliferative diabetic retinopathy (*Wetzig et al* 1963 1966 1967 *Okun* and *Cibis* 1966 *Amalric* and *Biau* 1967 *Guinan* 1967 *Mc Meel* 1967) all using the Zeiss Light Coagulator introduced by *Meyer Schwickerath* in 1954

Encouraged by these results a series of photocoagulation treatments on diabetics with proliferative diabetic retinopathy were started at the University Eye Clinic (Rigshospitalet) in Copenhagen

Material and Method

The series consists of 39 diabetics (46 eyes) all presenting proliferative diabetic retinopathy The photocoagulation was performed under local anesthesia using 2 per cent lidocain retrobulbar The pupil was maximally dilated before each

*) Presented at the U S Public Health Service Symposium on Treatment of Diabetic Retinopathy September 29 – October 1 1968 in Warrenton, Virginia U.S.A

Acknowledgement

The author is greatly indebted to Prof G Blom Inst of Math Statistics Lund for valuable advice

The work has been supported by the Swedish Medical Research Council

Abstract

Instantaneous visual acuity is defined and treated as a stochastic process The properties of this process can be studied indirectly in another realizable process This is generated by letting the outcome of a trial govern the diffi culty of the next object An analysis of this process makes it possible to deter mine if the mean and dispersion describe the visual performance satisfactorily or not

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6 *Krakau C E T* An automatic apparatus for *time series* analysis of visual acuity Vision Res Vol 7 (1967) p 99



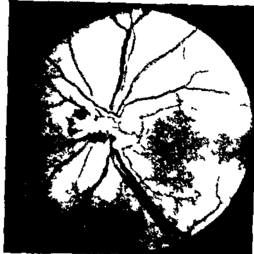


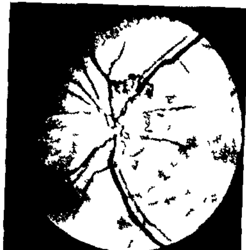


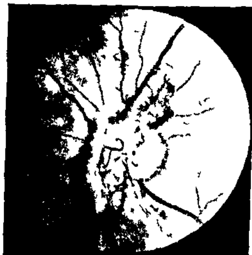
Fig 7
Advanced proliferative retinopathy
Fig 8
Pronounced degenerative changes in the hyaloid membrane
Fig 9
Vitreous detachment and retrovitreal hemorrhage

treatment The Zeiss Light Coagulator was used and from 5 to 20 photocoagulation burns were applied at each treatment The number of treatments varied from 1 to 5 at intervals from 2 to 3 months

At first overload power 1–2 with an aperture of 1.5 to 3 0 was used without filter but later normal power with apertures of 3 0 to 6 0 was used The small

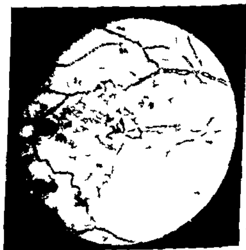












Figs 1 2 Pre and peripapillary neovascularization with a delicate stroma of connective tissue lying just preretinally

Figs 3 4 Pre and peripapillary neovascularization with connective tissue formation extending into the vitreous

Figs 5 6 Peripheral neovascularization with a delicate stroma of connective tissue lying just preretinally

Table 1

Average age 48 years Average duration of diabetes 25 years

Age	Sex	Age at diagnosis of diabetes	Age at first ocular symptoms	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Follow up period in months	Visual acuity at last examination	Classification of retinopathy at last examination
38	M	8	37	6 6	$N_1 F_1 H_3$	14	6/18	$N_0 F_0 H_0$
49	F	33	49	6/18	$N F_0 H_0$	8	6 12	$N_3 F_0 H_3$
8	M	36	55	6 12	$N_1 F_0 H_3$	13	6 9	$N_0 F_0 H_0$
47	M	12	4[illegible]	6/18	$N_1 F_0 H_3$	18	6 60	$N_0 F_1 H_3$
56	M	26	56	6 6	$N_1 F_0 H_0$	8	6 6	$N_0 F_0 H_3$
46	F	12	40	6 9	$N_1 F_0 H_3$	8	6 9	$N_0 F_0 H_3$
46	M	31	45	6 6	$N_1 F_0 H_3$	15	CF	H
51	M	23	51	<6 6	$N_1 F_0 H_3$	19	6 6	$N_0 F_0 H_3$
9	M	40	38	6/12	$N_1 F_0 H_3$	9	6 9	$N_0 F_0 H_0$
34	M	15	3	6 4	$N_1 F_0 H_0$	11	CF	H

Table 2

Average age 46 years Average duration of diabetes 23 years

Age	Sex	Age at diagnosis of diabetes	Age at first ocular symptoms	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Follow up period in months	Visual acuity at last examination	Classification of retinopathy at last examination
4[illegible]	F	29	4[illegible]	6 36	$N F H_3$	1	6 6	N F H
4[illegible]	M	31	4[illegible]	CF	$N_1 F_1 H_1$	10	CF	H
4[illegible]	F	[illegible]	43	<6 18	$N F H_3$	1	6 60	$N F H_1$
[illegible]	M	[illegible]	[illegible]	1 60	$N F H_0$	1	1 60	$N_1 F_0 H_1$
[illegible]	M	[illegible]	49	6 9	$N F H_0$	17	2 60	$N_1 F H_0$

aperture was preferentially used for making photocoagulation burns at the disc while the other apertures were used in the fundus periphery In all instances macula burns were avoided

Practically none of the patients were hospitalised but they were advised to remain in bed the first day after treatment and to limit their physical activity for approximately one to two weeks

The series was divided into 5 groups Group 1 comprises eyes with Neo vascularization extending from the disc and lying just prepapillary or peri papillary containing only a delicate supporting stroma (figs 1 – 2) Group 2 Peripapillary neovascularization extending into vitreous and containing a visible supporting stroma (figs 3 – 4) Group 3 Neovascularizations outside the disc area located *just preretinally and without any visible connective tissue (figs 5 – 6)* Group 4 Preretinal neovascularizations outside the disc area containing a certain amount of fibrous tissue Group 5 Cases with extensive fibrous tissue *formation (fig 7) pronounced degeneration of the hyaloid membrane (fig 8)* and vitreous collapse and retrovitreal hemorrhage (fig 9)

Classification of proliferative diabetic retinopathy

The following classification was used in this series

N *Neovascularization* F *Fibrous proliferation extending into vitreous*

H Vitreous hemorrhage

N_0 *No new formed vessels*

N_1 Four or fewer discreet patches or four or fewer disc areas of new vessels

N_2 Greater than *four discreet patches* or greater than four disc areas of new vessels

F_0 No fibrous proliferation extending into vitreous cavity (There may be some fibrous proliferation present but it is restricted to the surface of the retina)

F_1 Fibrous proliferation extends into the vitreous cavity but involves four or fewer discreet patches or four or fewer disc areas

F Greater than four descreet patches or greater than four disc areas of fibrous proliferation extending into the vitreous

H_0 No vitreous hemorrhage

H_1 Presence of vitreous hemorrhage but the retina can be seen well enough to be classified

H This category describes eyes with vitreous hemorrhage which is so extensive that the retina cannot be seen well enough to be classified

Results

The results of photocoagulation in group 1 are listed in table 1 and fundus photographs from a patient in this group before and after treatment are shown in figs 10 and 11

Table 1

Average age 48 years Average duration of diabetes 25 years

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49	F	33	49	6/18	$N F_0 H_1$	8	6 1?	$N_0 F_0 H_0$
58	M	36	55	6/12	$N_1 F_0 H_0$	13	6 9	$N_0 F_0 H_0$
47	M	1?	46	6 18	$N_1 F_0 H_1$	18	6 60	$N_1 F_1 H_1$
56	M	6	56	6 6	$N_1 F_0 H_1$	8	6 6	$N_0 F_0 H_0$
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51	M	23	51	<6 6	$N_1 F_0 H_1$	19	6 6	$N_0 F_0 H_1$
59	M	40	58	6/12	$N_1 F_0 H_1$	8	6 9	$N_0 F_0 H_0$
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[illegible]	M	[illegible]	[illegible]	1 60	$N F H_1$	1	1 60	$N_0 F_0 H_1$
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Table 3

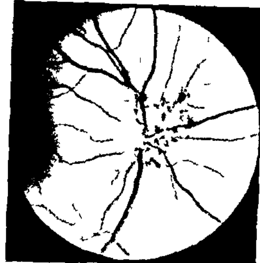
Average age 34 years Average duration of diabetes 20 years

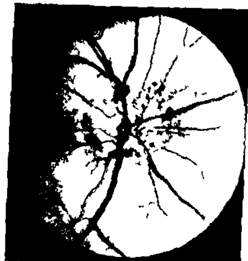
Age	Sex	Age at diagnosis of diabetes	Age at first ocular symptoms	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Follow up period in months	Visual acuity at last examination	Classification of retinopathy at last examination
28	F	4	27	6 6	$N\ F_0 H_0$	10	<6/6	$N_0 F_0 H_0$
9	F	4	27	6 6	$N\ F_0 H_0$	8	<6.6	$N_0 F_0 H_0$
24	M	10	[illegible]	6 1?	$N\ F_0 H_0$	8	HM	H
28	F	6	27	6 6	$N_1 F_0 H_1$	8	6 6	$N_0 F_0 H_0$
43	M	20	42	6 9	$N_1 F_0 H_0$	13	6 9	$N_0 F_0 H_0$
53	M	43	52	6 60	$N\ F_0 H_1$	13	6 60	$N_1 F_0 H_0$
27	M	7	26	6.9	$N\ F_0 H_0$	16	6.60	$N\ F_0 H_1$
28	M	10	27	6 18	$N\ F_0 H_1$	9	6.9	$N_1 F_0 H_0$
37	M	15	36	6 9	$N\ F_0 H_0$	9	6/24	$N_0 F_1 H_0$
5	F	8	24	6 9	$N_1 F_0 H_0$	8	6 9	$N_0 F_0 H_0$
34	M	16	31	6/12	$N_1 F_0 H_0$	13	<6.6	$N_0 F_0 H_1$
29	F	16	26	6/12	$N\ F_0 H_0$	15	6/18	$N_0 F_1 H_1$
46	M	8	46	6 6	$N\ F_0 H_0$	8	6.6	$N_0 F_0 H_0$
46	M	8	45	6.12	$N\ F_0 H_0$	10	6.6	$N_0 F_0 H_0$
51	M	23	51	<6.6	$N_1 F_0 H_0$	17	6 6	$N_0 F_0 H_0$
41	M	21	41	6 6	$N\ F_0 H_0$	9	6 6	$N_0 F_0 H_0$
[illegible]	M	7	24	6.6	$N\ F_0 H_0$	21	6.6	$N_0 F_0 H_0$
6	F	10	25	6 6	$N_1 F_0 H_0$	8	6.6	$N_0 F_0 H_0$
37	M	19	31	6 6	$N_1 F_0 H_0$	14	6 6	$N_0 F_0 H_0$
37	M	19	32	6.6	$N\ F_0 H_0$	8	6 6	$N_0 F_0 H_0$

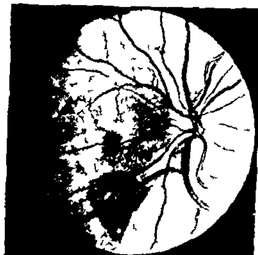
Table 4

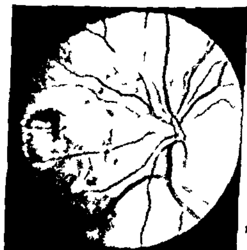
Average age 45 years Average duration of diabetes 20 years

Age	Sex	Age at diagnosis of diabetes	Age at first ocular symptoms	Visual acuity prior to photocoagulation	Classification of retinopathy prior to treatment	Follow up period in months	Visual acuity at last examination	Classification of retinopathy prior last examination
41	M	1	41	6 6	$N\ F_1 H_1$	13	6 6	$N_0 F_1 H_0$
[illegible]	M	20		6.12	$N\ F_1 H_1$	9	6 9	$N_0 F_1 H_1$
[illegible]	M	15	[illegible]	[illegible]	$N\ F_1 H_0$	13	6 9	$N_0 F_1 H_0$
[illegible]	M	4	34	[illegible]	$N\ F\ H_0$	9	6 36	$N_1 F\ H_1$
[illegible]	M	43	5	[illegible]	$N_1 F_1 H_0$	8	6 18	$N_0 F_1 H_0$













Figs 10 11 12 13 and 14 15
Same eye Before and after treatment with photocoagulation

cause traction in the retina or arcuate scotomas converting these cases into visual failures even though the neovascularization is destroyed

The average follow up period this series is about 12 months making it too short to draw any conclusions as to the long term prognosis of treatment of proliferative diabetic retinopathy by photocoagulation

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The results of treatment in group 2 are listed in table 2

The results of treatment in group 3 are listed in table 3 and fundus photographs from a patient in this group before and after treatment are shown in figs 12 and 13

The results of treatment in group 4 are listed in table 4 and fundus photographs from a patient in this group before and after treatment are shown in figs 14 and 15

All 6 cases in group 5 were failures

Complications

Large retinal preretinal or vitreous hemorrhage occured in 4 of our cases within 2 months after treatment I 2 cases gross hemorrhage occurred in both eyes some days after the photocoagulation This hemorrhage is considered to be due to chance and unrelated to treatment, and the same is considered to be the case in 4 more patients who developed vitreous hemorrhage more than 2 months after treatment

Arcuate scotomas were usually present just after the photocoagulation burn After some time however scotomas corresponded only to the fundal scar produced by the photocoagulation except in 2 cases where treatment had been *too violent*

In 3 cases traction in the retina by the chorioretinal scar produced made *the morphologically good result a visual failure*

Retinal detachment was not observed in group 1 to 4 but occured in group 5

Conclusion

This series showed that neovascularization in the early stages of proliferative diabetic retinopathy can be destroyed succesfully by photocoagulation while later stages and especially those cases with extensive fibrous tissue formation did not react favorably

It must be stressed however that photocoagulation is a palliative treatment which does not cure the disease New vascular proliferations may occur sooner or later after successful occlusion of neovascularizations which also occurred in this series The patients must therefore be followed up at intervals and treated again if necessary

Care should be taken not to produce too heavy burns which later on may

same type of fibrils as those found in the exfoliation substance on the lens capsule were also observed in the internal limiting membrane of the iris and on the pigment epithelium of this structure They found a pathological layer the so called amorphous layer in the peripheral part of the lens capsule *between the epithelium and the fibrillary layer* These workers advanced the theory that senile exfoliation of the anterior lens capsule was produced by secretion from the lens epithelial cells (fibrillopathia epitheliocapsularis) but emphasized also the pigment epithelium of the iris as a possible source of this substance

Independently *Ashton Shakib Collyer* and *Blach* (1965) described in lenses with exfoliation material the same pathological lens capsule layer but found an apparantly normal lens epithelium *Shakib Ashton* and *Blach* (1965) found this material also in the internal limiting membranes of the iris and ciliary body and around the iris vessels They thought it was most likely that the exfoliation material was an abnormal substance from the aqueous which either filtered through the blood aqueous barrier or which was elaborated locally The lens epithelium however is mentioned as a possible source of this substance

If the substance is not formed from the lens then it should be possible in some eyes to find it on other structures but not on the lens or at any rate in smaller quantities on the lens than other places The object of this study was to examine this possibility further and to investigate in persons with unilateral exfoliation whether there was any evidence in the "normal eye of the capsule changes described previously in eyes with exfoliation (Bertelsen Drablos and *Flood* 1964 *Ashton Shakib Collyer* and *Blach* 1965)

Material and Methods

The material collected at Ullevål Hospital Oslo and investigated at the Department of Ophthalmology University of Bergen comprised 100 eyes from 50 persons over 70 years of age 22 men and 28 women None of them had had any known eye disease However the intraocular pressure had not been measured ante mortem The material with age and sex distribution, is presented in Table 1

The eyes were removed on average 15 hours after death They were immersed in a 4 per cent formaldehyde solution and within 3 hours examined with a slit lamp after the cornea had been removed The same technique was used as described by *Sunde (19*[illegible]*)* Thence they were further fixed in a 4 per

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SENILE EXFOLIATION (PSEUDO EXFOLIATION FIBRILLOPATHIA EPITHELIO CAPSULARIS) OF THE LENS CAPSULE IN A POSTMORTEM MATERIAL

Microscopic investigation of 100 eyes

BY

JON S LARSEN

The general opinion during the last years has been that the so called senile exfoliation of the lens capsule (*Vogt* 1931) in reality was caused by a precipitate from the aqueous humor (*Busacca* 1928 *Dvorak-Theobald* 1954 *Sunde* 1956 *Landolt* 1957 *Arnesen Sunde* and *Schulz-Haudt* 1963) Therefore *Dvorak Theobald* (1954) called this condition pseudo exfoliation of the lens capsule

Several workers are of the opinion that this substance is due to pathological changes in the uvea (*Malling* 1938 *Goldmann* 1957 *Amsler* 1957 *Joannides Katsourakis* and *Velissaropoulos* 1961)

Gifford (1957) put forward the theory that the exfoliation material was derived from a degenerative process of the zonular lamella on the lens and the zonular fibres but he believed that the substance could also be formed on the posterior surface of the iris and on the ciliary body from a reticulin membrane on the surface of these structures

In 1964 *Bertelsen Drablos* and *Flood* discovered in eyes with senile exfoliation characteristic changes in the lens capsule and lens epithelial cells The

same type of fibrils as those found in the exfoliation substance on the lens capsule were also observed in the internal limiting membrane of the iris and on the pigment epithelium of this structure They found a pathological layer the so called amorphous layer in the peripheral part of the lens capsule between the epithelium and the fibrillary layer These workers advanced the theory that senile exfoliation of the anterior lens capsule was produced by secretion from the lens epithelial cells (fibrillopathia epitheliocapsularis) but emphasized also the pigment epithelium of the iris as a possible source of this substance

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If the substance is not formed from the lens then it should be possible in some eyes to find it on other structures but not on the lens or at any rate in smaller quantities on the lens than other places The object of this study was to examine this possibility further and to investigate in persons with unilateral exfoliation whether there was any evidence in the normal eye of the capsule changes described previously in eyes with exfoliation (Bertelsen Drablos and *Flood* 1964 *Ashton Shakib Collyer* and *Blach* 1965)

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Table 1
Composition of material and distribution of exfoliation substance

	No of cases	No of eyes	Age in years				
			70–74	75–79	80–84	85–89	90–94
Men	22	44	9	6	5	1	0
F	28	56	11	6	4	6	2
Total	50	100	20	12	9	7	2
Men with exf	4	4	2	1	1		
F with exf	2	4	1			1	
Men + F with exf	6	8	3	1	1	1	

cent formaldehyde solution with 5 per cent mercuric chloride dehydrated in alcohol cleared in chloroform and embedded in paraffin In all 598 sections were examined with a minimum of 4 from each eye The sections were distributed from the center to the periphery of the lens Masson s trichrom *stain* was used as standard method with supplementary haemalun erythrosin saffran (H E S) haematoxylin eosin (H E) and periodic acid Schiff (P A S)

Results

Slit lamp investigation A central exfoliation disc was found unilaterally on the lens in 2 persons In a third person flakes were observed at the edge of the pupil in one eye The exfoliation material in these 3 eyes was later confirmed microscopically but the central disc could not be verified presumably because it had been washed away during preparation of the sections

Microscopic examination Exfoliation material was found in 8 eyes Unilateral changes were present in 4 men and bilateral changes in 2 women In all the eyes with exfoliation there were typical excrescences on the anterior *surface*

of the lens as well as on the zonular fibres the posterior surface of the iris the ciliary processes and the hyaloid membrane However the histological sections revealed that most of the exfoliation material was located on the anterior surface of the lens The substance had the same structure and form irrespective of its localization a bush like formation which seemed to be anchored to the underlying surface

On the anterior surface of the lens most of the exfoliation material with the appearance of classic exfoliation excrescences was always found corresponding to the peripheral exfoliation band In all the eyes there was little of this material at the periphery of the lens from the area where the zonular fibres are attached medially and to the equator but even here there were diffuse excrescences in all 8 eyes Changes in the capsule in the form of the cara teristic amorphous layer (Fig 1) were observed in all eyes with exfoliation Exfoliation free eyes even in persons with unilateral exfoliation did not reveal the amorphous layer of the lens capsule The amorphous layer was always localized to the equatorial or pre equatorial part of the lens capsule Often this



Fig 1

Am th u l y A f haracteristic appearance in the lens capsule at the pre equat l reg n Small d s are seen in the fibrillar layer (F) Epithelium (E) On th face remains f exfoliati n substance Masson Trichrome × 1500

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Fig °
Exfoliation aggregate (E) on ciliary process Masson Trichrome × 600



Fig 8
Exfoliation excrescences on the hyaloid membrane (M) Masson Trichrome × 600

layer was not continuous but dispersed in thin spindleshaped patches It was however always in close contact with the epithelium

Next to the anterior surface of the lens the largest piling up of exfoliation material seemed to be on the zonular fibres where the accumulation was generally speaking very even often like frost crystals on a string Here the substance was built up of either large or small excrescences which seemed *essentially to have the same* appearance as on the anterior surface of the lens but as a rule it had a thinner bush like configuration Occassionally however the exfoliation material on the zonular fibres was in the form of larger aggregates

Large detached exfoliation aggregates were sometimes discovered between the zonular fibres and beyond them in the posterior chamber In the central part of the aggregates the substance was more homogeneous and compact but *otherwise it was of similar structure and was stained as the typical excrescences* which were only to be seen on the surface of these formations

On the posterior surface of the iris and on the ciliary processes the exfoliation material predominantly showed the same morphology as on the anterior surface of the lens and the zonular fibres However as a rule the excrescences on these structures seemed to have a broader anchorage to underlying structures than they had on the anterior surface of the lens and the zonular fibres Large exfoliation aggregates were also observed on the ciliary processes in isolated sections in 2 eyes Here the aggregates either had a broad solid anchorage (Fig 2) or they were small and band like

The excrescences on the hyaloid membrane appeared generally smaller than those on other structures They seemed to be relatively loosely attached to the membrane and sometimes the *exfoliation material lay close up to the membrane* and sometimes the exfoliation material lay close up to the membrane without any connection to it like broken off bushes (Fig 3) Such fragments of exfoliation substance were sometimes also to be found on the anterior surface of the lens and on the other structures – but only sporadically On the other hand in several sections detached fragments of excrescences could be seen *in* large numbers lying free in the posterior chamber

Discussion

Of the individuals investigated 12% had senile exfoliation 8% unilateral *and* 4% bilateral The material is too small to give any definite indication of the frequency of exfoliation There is no comparable histological material *Horven* (1935) found an exfoliation frequency of 6 2% in 65 inmates all over

exfoliation material during the preparation of the sections with the microtome

According to earlier electron microscopic studies (*Bertelsen Drablos* and *Flood* 1964) there are reasons for supposing that the lens epithelium can possibly play a decisive part in the production of the exfoliation substance Whether this substance can also be produced in other parts in the eye and whether this process can proceed simultaneously are questions which still have not been cleared up

Hypothetically it is possible that typical exfoliation excrescences are not always formed in the peripheral part of the lens capsule but that the substance may leave the capsule in the form of microfilaments or in a molecular form which can precipitate and gradually build up the caracteristic excrescences on the various structures in the posterior chamber

The anatomical relationship in the posterior chamber with the almost membrane like form of the zonular fibres give reason for supposing that special flow conditions may exist and that the exfoliation material does not slavishly have to follow the main stream of the aqueous flow If this thought is followed it is also possible that the building up of exfoliation substance on the anterior surface of the lens could to some extent, proceed in the same way For example this can apply to the substance in the medial part of the peripheral exfoliation band where the amorphous layer is often absent and in the central disc

Summary

100 presumably healthy eyes from 50 individuals over 70 years of age were examined microscopically So called senile exfoliation was found in 12% of those examined

The exfoliation material did not seem to prefer any particular structure in the posterior chamber but the major part of this substance appeared always to be on the lens capsule

Pathological lens capsule changes in form of the amorphous layer were found in all eyes with exfoliation but in none of the exfoliation free eyes not even in the normal eye from individuals with unilateral exfoliation Therefore the amorphous lens layer seems to be pathognomonic for eyes with senile exfoliation

The morphology of the exfoliation material and its distribution on the various structures in the posterior chamber are discussed The author believes that the caracteristic exfoliation excrescences are built up "on the spot" even though the material can possibly originate from the lens epithelium

60 years of age, residing in an old people's home In a mass investigation in Bergen Norway *Aasved* (1968) *found a frequency of 6 8 %* in a material of 649 persons over 70 years of age examined with a slitlamp under mydriasis

In all the eyes with exfoliation the substance was seen on the zonular fibres ciliary body posterior surface of the iris and on the hyaloid membrane as well as on the anterior surface of the lens When this subsance is first demonstrable microscopically it does not seem to be selectively located to any particular one of these structures However in all the eyes the amount of exfoliation material appeared to be greatest on the lens capsule

Sunde (1956) believed that the exfoliation excrescences originated locally and did not *consist of pre existing formations detached from one structure and* removed to another The observations made of the present study support this view The excrescences appeared to be anchored to the underlying elements and detached fragments represented only a small amount of the exfoliation material in this respect and were of minor importance quantitatively

There is reason to suppose that the detachment of excrescences may to some extent be caused by movements of the iris against the lens or traumatisation of the eye in connection with enucleation

In 18 lenses with exfoliation *Bertelsen Drablos* and *Flood* (1964) demonstrated the amorphous layer in intimate contact with the lens epithelium *Ashton Shakib Collyer* and *Black* (1965) described this layer which was in contact with the lens epithelium in 5 lenses with this substance *Horven I* (1966) found in 10 out of 11 exfoliation lenses an amorphous layer but believed that in 2 lenses he could demonstrate this layer in the middle of the lens capsule without any contact with the lens epithelium

In this investigation the amorphous layer was always found to be in close contact with the epithelium and localized to the equator and pre equatorial area and it was only found in the 8 lenses with exfoliation The amorphous layer in a few sections from 2 eyes seemed apparently to be lying in the middle of the lens capsule In reality however these appearances were due to an incomplete staining of the amorphous layer This layer in other sections from the same eyes was discovered in distinct contact with the lens epithelium

Corresponding to investigations carried out up to now the amorphous layer is *only found in the peripheral part of the anterior* capsule of the lens where epithelial cell activity is greatest but where fairly often little exfoliation material is found (*Sunde* 1956 *Tarkkanen* 1962) Occasionally however plentiful of exfoliation material is observed in this area of the lens capsule (*Ashton Shakib Collyer* and *Black* 1965) The zonular lamella probably only exists at the equator and in the region surrounding it (*Ley Holmberg* and *Yamashita* 1960 *Ashton Shakib Collyer* and *Black* 1965) The reason for the spare *amount of exfoliation substance* in this area found in the present study can possibly depend on a mechanical removal of the zonular lamella together with

exfoliation material during the preparation of the sections with the microtome

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Summary

100 presumably healthy eyes from 50 individuals over 40 years of age were examined microscopically So called senile exfoliation was found in 12% of those examined

The exfoliation material did not seem to prefer any particular structure in the posterior chamber but the major part of this substance appeared always to be on the lens capsule

Pathological lens capsule changes in form of the amorphous layer were found in all eyes with exfoliation but in none of the exfoliation free eyes not even in the normal eye from individuals with unilateral exfoliation Therefore the amorphous lens layer seems to be pathognomonic for eyes with senile exfoliation

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THE PRESSURE LOWERING EFFECT OF ASCORBIC ACID IN OCULAR HYPERTENSION

BY

ERIK LINNÉR

In previous studies I reported that ascorbic acid *produced* a fall in the intraocular pressure of about 2 mm Hg[illegible]. The pressure lowering *effect* was obtained after oral administration and also after topical application. The fall in pressure took place about two days *following* the administration of ascorbic acid. So far normal human eyes and a few glaucomatous eyes have been studied.

In the first study of normal human eyes there was found to be a slight numerical increase in the facility of *outflow* of about 15 per cent. *The reduction* in the outflow pressure of about 50 per cent could hardly be *entirely* explained by these tonographic changes. Other possible mechanisms were *therefore* discussed. A reduction *in* the rate of aqueous flow was considered to be the most likely explanation. In further studies *the* results obtained by means of the suction cup technique *indicated* a diminished increase *in* pressure and volume during treatment with ascorbic acid. These results supported the explanation that the pressure fall was caused by a reduction *in* the rate of aqueous flow. This is however true *only* under the assumption that *no other* pathways exist by which the aqueous humour can leave the eye. A bulk drainage by way of uveo-scleral routes *in* addition to the conventional routes as reported by Bill cannot be excluded although such pathways have *not* been demonstrated in human eyes. According to this *suggestion* an increase in the drainage through the posterior part of the eye might occur *if the* hyaluronic acid in the posterior part of the eye was depolymerized by *the* high concentration of *ascorbic* acid.

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Table 1

Effect of ascorbic acid on intraocular pressure (Schiotz) (P_0) and facility of outflow (C) in 25 subjects with ocular hypertension 0.5 gm ascorbic acid was given four times a day by mouth for 6 days

		Before ascorbic acid I	During ascorbic acid II	Difference II I
P_0	$\bar{x}$	23.3	22.2	−1.10
	$s_{\bar{x}}$	0.[illegible]1	0.69	0.299
C	$\bar{x}$	0.23	0.20	−0.024
	$s_{\bar{x}}$	0.015	0.014	0.0098

In comparison to the difference between the two eyes before treatment the pressure value was significantly lower in the test eye than in the control eye during treatment with eye drops of ascorbic acid the change being 1.19 mm Hg (Table 2)

The pressure lowering effect was of the same order of magnitude following systemic and topical treatment with ascorbic acid

Discussion

The fall in pressure previously demonstrated in normal human eyes was also found in the subjects with *ocular hypertension* in this study The effect was of

Table 2

Effect of 10% ascorbic acid given topically 3 times daily during 3 days on the intra ocular pressure (Schiotz) in 19 individuals with ocular hypertension.

	Before ascorbic acid		Ascorbic acid		Difference
	Test eye I	Control eye II	Test eye III	Control eye IV	(III IV) (I II)
$\bar{x}$	[illegible]3.7	23.1	2[illegible].8	23.4	1.19
$s_{\bar{x}}$	0.9	1.0[illegible]	0.9	1.0	0.346

41

The purpose of the present study was to investigate the effect of ascorbic acid on a *group of human beings with ocular hypertension* In these cases the intraocular pressure was 20 25 mm Hg and the outflow pressure about 10 15 mm Hg instead of about 5 mm Hg at normal pressure levels

Material and Methods

The individuals in this study belonged to a group in whom moderate ocular hypertension was detected They have been kept under observation for five years without treatment Two reports concerning this follow up were published[8 9]

One group of 25 subjects with an average age of 63 years was first examined by tonography without treatment A new tonographic examination was then carried out after administration of ascorbic acid by mouth 0 5 gm four times a day for six days The mean of the two eyes was used in all calculations as a representative value for each individual The difference between the values during and before treatment was calculated for each individual

In a separate group of 19 subjects with an average age of 63 years the intra ocular pressure was measured by means of the same electronic tonometer and recorder A 10 *per cent aqueous solution of ascorbic acid was given topically* in one eye three times a day for 3 days and the other eye was used as a control* The right and the left eye were treated in alternate subjects The effect of the treatment was calculated for each individual as the change in the difference between the test eye and the control eye following topical application of ascorbic acid The differences are greater in ocular hypertension than in eyes with normal pressure

A certified Schwarzer s electronic tonometer and a Philips recorder were used The right eye was always examined before the left one The *facility* of outflow was calculated on the first four minutes of the tracing using Friedenwald s table of 1955 Benoxinate 0 4 per cent (Novesin Wander Berne) was used as a *local anaesthetic*

Results

Following oral treatment with ascorbic acid a significant fall in the intraocular pressure of 1 10 mm Hg was found but no significant change in the facility of outflow was observed (Table 1)

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* These drops were kindly prepared by AB Hassle Goteborg Sweden

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Discussion

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Table 2

Effect of 10% ascorbic acid given topically 3 times daily during 5 days on the intra ocular pressure (Schiotz) in 19 individuals with ocular hypertension.

	Before ascorbic acid		Ascorbic acid		Difference
	Test eye I	Control eye II	Test eye III	Control eye IV	(III IV) (I II)
x	23.7	23.1	22.8	23.4	1.19
s_x	0.97	1.02	0.97	1.05	0.346

The purpose of the present study was to investigate the effect of ascorbic acid on a group of human beings with ocular hypertension In these cases the intraocular pressure was 20 25 mm Hg and the outflow pressure about 10 15 mm Hg instead of about 5 mm Hg at normal pressure levels

Material and Methods

The individuals in this study belonged to a group in whom moderate ocular hypertension was detected They have been kept under observation for five years without treatment Two reports concerning this follow up were published[8 9]

One group of 25 subjects with an average age of 63 years was first examined by tonography without treatment A new tonographic examination was then carried out after administration of ascorbic acid by mouth, 0 5 gm four times a day for six days The mean of the two eyes was used in all calculations as a representative value for each individual The difference between the values during and before treatment was calculated for each individual

In a separate group of 19 subjects with an average age of 63 years the intraocular pressure was measured by means of the same electronic tonometer and recorder A 10 per cent aqueous solution of ascorbic acid was given topically in one eye three times a day for 3 days and the other eye was used as a control The right and the left eye were treated in alternate subjects The effect of the treatment was calculated for each individual as the change in the difference between the test eye and the control eye following topical application of ascorbic acid The differences are greater in ocular hypertension than in eyes with normal pressure

A certified Schwarzer s electronic tonometer and a Philips recorder were used The right eye was always examined before the left one The facility of outflow was calculated on the first four minutes of the tracing using Friedenwald s table of 1955 Benoxinate 0 4 per cent (Novesin Wander Berne) was used as a local anaesthetic

Results

Following oral treatment with ascorbic acid a significant fall in the intraocular pressure of 1 10 mm Hg was found but no significant change in the facility of outflow was observed (Table 1)

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* These drops were kindly prepared by AB Hassle Goteborg Sweden

Table I

Effect of ascorbic acid on intraocular pressure (Schiotz) (P_o) and facility of outflow (C) in ‿5 subjects with ocular hypertension 0 5 gm ascorbic acid was given four times a day by mouth for 6 days

		Before ascordic acid I	During ascorbic acid II	Difference II I
P_o	x	?3 3	22 2	— 1 10
	s_x	0 71	0 69	0 299
C	x	0 23	0 20	— 0 024
	s_x	0 015	0 014	0 0098

In comparison to the difference between the two eyes before treatment the pressure value was significantly lower in the test eye than in the control eye during treatment with eye drops of ascorbic acid the change being 1 19 mm Hg (Table 2)

The pressure lowering effect was of the same order of magnitude following systemic and topical treatment with ascorbic acid

Discussion

The fall in pressure previously demonstrated in normal human eyes was also found in the subjects with ocular hypertension in this study The effect was of

Table 2

Effect of 10 % ascorbic acid given topically 3 times daily during 3 days on the intra ocular pressure (Schiotz) in 19 individuals with ocular hypertension.

	Before ascorbic acid		Ascorbic acid		Difference
	Test eye I	Control eye II	Test eye III	Control eye IV	(III IV) (I II)
x	3 7	?3 1	2‿8	?3 4	1 19
s_x	0 97	1 02	0 97	1 0ɔ	0 346

the same order of magnitude in spite of a marked difference in outflow pressure The tonographic values of outflow facility were not significantly changed These results are further evidence in support of the view that the fall in pressure could not be explained by a change in the outflow facility

The findings in this study confirm the conclusion that the fall in pressure could be caused by a reduction in the rate of aqueous flow or as another possibility which cannot be excluded by bulk drainage by way of posterior uveo scleral routes At the moment there is no way of distinguishing between a change in a pressure independent uveo scleral drainage and a change in the rate of aqueous flow entering the anterior chamber in human eyes

In a paper by Gnadinger and Willome[3] the effect of topical application of a 10 per cent solution of ascorbic acid was examined According to their figures there was a difference of 1 5 mm Hg in the mean value before and during application of ascorbic acid in the control eye this difference was 0 57 mm Hg The authors reported that the treated and the untreated eye did not differ significantly, but they did not present the differences within each individual The mean value of the fall in pressure was about 1 mm Hg greater in the treated eye than in the control eye and this effect is of the same order of magnitude as the results in the present study

In a review Bietti[1] reported different studies concerning the pressure reducing effect of ascorbic acid Doses as high as 0 1 to 0 5 gram per kilogram body weight were given by mouth or 0 4 to 1 0 gram per kilogram intravenously A marked fall of the intraocular pressure was observed within a few hours This result was considered to be caused by an osmotic effect at least in rabbits Other possible pressure reducing mechanisms were also investigated by using tonography In most of the cases a diminished formation of aqueous humour rather than a decrease in the outflow resistance was considered to play a role although the possibility of the resistance being reduced was not completely excluded in some cases Their conclusion that the tonographic evidence speaks in favour of a decrease in the rate of aqueous flow rather than a change in outflow facility is in agreement with my findings

Summary

The effect of ascorbic acid on human beings with ocular hypertension was examined

Following oral treatment with 2 gram of ascorbic acid daily for 6 days the intraocular pressure decreased significantly 1 10 mm Hg but no significant change in the facility of outflow was observed Following topical administration

of ascorbic acid the pressure in the test eye was significantly lower than the pressure in the control eye in comparison to the difference between the two eyes before treatment

The findings in this study confirm the conclusion that the fall in pressure could be explained by a reduction in the rate of aqueous flow or as another possibility which cannot be excluded by bulk drainage by way of posterior uveo scleral routes

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The findings in this study confirm the conclusion that the fall in pressure could be caused by a reduction in the rate of aqueous flow or as another possibility which cannot be excluded by bulk drainage by way of posterior uveo scleral routes At the moment there is no way of distinguishing between a change in a pressure-independent uveo scleral drainage and a change in the rate of aqueous flow entering the anterior chamber in human eyes

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Following oral treatment with 2 gram of ascorbic acid daily for 6 days the intraocular pressure decreased significantly 1 10 mm Hg but no significant change in the facility of outflow was observed Following topical administration

the observation periods thus ranging from 4 to 15 years At this point of time 25 patients had died while 12 were still alive Of the latter 10 were followed up by the author while two did not appear The data concerning these are therefore derived from the case report On the follow up examination the patients were subjected to measurement of vision slit lamp examination measurement of tension examination for motility and of pupil and ophthalmoscopy in mydriasis

None of the patients had been examined by the author at the acute stage The descriptions in the case records being not equally detailed the material is unsuitable for an analytical assessment of all the ophthalmoscopic changes at the acute stage of the central artery occlusion Such an investigation was undertaken by *Coverdale* (1929) who collected 11 cases of occlusions of the retinal arterioles though he did not concentrate solely on the central artery

Sex The series comprised as stated 21 males and 16 females Of the 12 followed up nine were men and three women and of the 25 dead at the time of the follow up 12 were men and 13 women

Age The mean age at the onset of occlusion was 63 0 years for the total series of 37 patients The mean age was lower 59 8 for the 12 followed up (youngest 37 and oldest 84) For the 25 patients dead at the time of the follow up the mean age was 64 6 at the onset of the occlusion (youngest 42 and oldest 83)

Table 1 shows the age distribution in 10 year age groups for the patients followed up the dead and the total series

Table 1
Age distribution at onset of occlusion in 10 year age groups

age group	men		women		men plus women		total series
	followed up	dead	followed up	dead	followed up	dead	
30 39			1		1		1
40 49	1	3		1	1	4	5
50 59	2	3	1		3	3	6
60 69	3	3	1	4	4	7	11
70 79	2	3		6	2	9	11
80 89	1			2	1	2	3
Total	9	12	3	13	12	25	37

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HOLGER EHLERS
ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the Eye Department Municipal Hospital Copenhagen
(Heads Professor P Brændstrup M D and Chief surgeon M S Norn M D)

OCCLUSION OF THE CENTRAL RETINAL ARTERY

A Follow Up

BY

S E LORENTZEN

The object of the present study has been to contribute towards clarifying the clinical picture in total occlusion of the central retinal artery This was done by following up all the patients with this diagnosis recorded within a 12 year period (1950 1961 incl) in the Department of Ophthalmology Kommunehospitalet Copenhagen

In addition to the prognosis of vision for these patients it was considered a matter of interest to throw some light on possible concurrent cardiovascular diseases and the influence of these on the life prognosis In other words the question suggested itself whether the vascular defect of the eye is an isolated phenomenon or forms part of a general cardiovascular disease (arteriosclerotic hypertensive) which shortens the life of these patients

Material

The series under review comprised 37 individuals (21 males and 16 females) with total central artery occlusion examined and recorded in the Department of Ophthalmology *Kommunehospitalet* Copenhagen 1950 1961 incl some as out patients and some during stay in hospital The follow up took place in *1964*

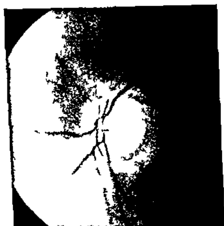




Fig 1

Left Fundus at the follow up of one of the patients with occlusion of the central retinal artery

Right Normal fundus

The 12 followed up had a mean age of 67 8 at this point of time the mean observation period being thus 8 0 years The 25 deceased patients had a mean age at death of 70 1 The average life time after the onset of occlusion was thus 5 5 years Does this average life time after the onset of central artery occlusion in this series correspond to that calculated for the "normal population" or is it shorter The average calculated mean life for the 25 deceased patients at the onset of occlusion was computed from the individual calculated mean life times at the occlusion, based on Danish population statistical calculations (*Statistisk Arbog* 1967) reckoned from the experience gained during the years 1956 1960 An average calculated mean life of 15 4 years was thereby arrived at against an actual average mean life of 5 5 years after the onset of occlusion

The 25 deceased patients with central artery occlusion thus presented a rather considerable excess mortality compared with the "normal population

By similarly computing the average calculated mean life at the time of occlusion for the group of patients followed up (12), this was found to be *18 9* years or considerably longer than the observation period of 8 0 years

For the whole series (37 patients) the calculated mean life at the *time of occlusion* was correspondingly 16 6 years

Eye affected The right eye was affected by occlusion in 22 cases and the left in 15 in other words a minor preponderance of right eye affection Central vein occlusion is most frequent in the left eye (*Brændstrup* 1950) but not so central artery occlusion *to judge from the present series* *Liversedge* & *Smith* (1962) found the right eye affected in 39 the left eye in 39 and six bilateral cases *among 84 patients with central retinal artery occlusion*

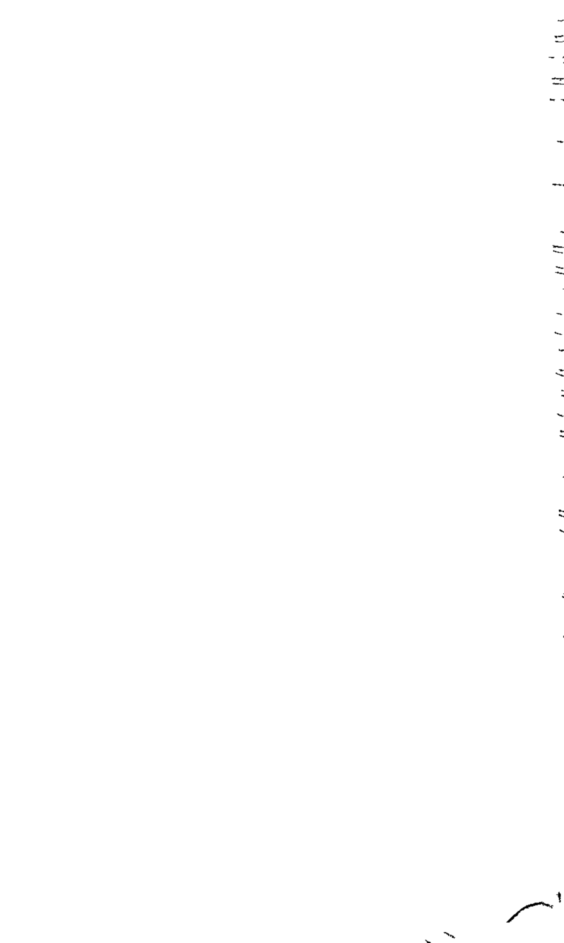
No unquestionable cases of bilateral occlusions of the central artery occurred *in the series under review*

Time of and activity at onset of occlusion For 18 patients we know the time of the day when the occlusion set in This shows an even spread over the day hours from 6 a m to 12 p m Seven cases occurred within the first quarter of the day five within the second and five within the third while only one came on during the night hours A similar equal distribution was observed by *Coverdale* (1929)

The central vein occlusions are stated frequently to be present on awakening in the morning (*Ehlers* 1967) They must in such cases have come on during sleep This may be related to a nocturnal fall in blood pressure with a consequent reduced blood flow

The series under review showed nothing to suggest a relationship between the central artery occlusion and particularly straining physical activity

Similarly was noted by *Coverdale* (1929) In only one case of the present se



ries had the occlusion come on in relation to a physical effort the patient having bent forward to sweep In none of the other eight cases in which the activity at the time of occlusion is known had this been particularly intensive Two patients were reading one sitting and the other lying In one the occlusion occurred on awakening after a nap and in one after a day s sleep following night work In one the occlusion came on in a tram and in one during cooking in one while riding a bicycle and in one during ordinary work (bricklaying)

Symptoms Occlusion of the central artery involves a sudden loss of vision In a few instances it is preceded by short periods with everything swimming before the eyes dimness of vision or short attacks of blindness obscurations Precursive symptoms had been experienced by two of the patients followed up (Within the group of deceased our information on such is inadequate for assessment) One a woman who experienced central artery occlusion of the right eye at the age of 37 had a few days before had obscurations of this eye In the other a man aged 60 the occlusion had been preceded six months previously by ten attacks of visual blurring each lasting 20 minutes None of these two patients developed neurological symptoms as described later in this paper but the latter who had intermittent claudication experienced three years later occlusion of the left femoral artery which led to amputation including the thigh

Among *Coverdale* s (1929) previously mentioned 11 patients all examined shortly after the onset of occlusion only one had noticed previous obscurations In this patient the occlusion was bilateral

Temporary loss of vision amaurosis fugax is a frequent symptom in carotid insufficiency *Hollenhorst* (1959) noticed it more often among patients with carotid insufficiency than among patients with carotid thrombosis

Vision On examination in the Department soon after the occlusion the 25 deceased patients had had the visual acuity of the affected eye seen in table 2

It is worth noting that the relatively good vision of the patient with 6/12 was due to presence of two cilioretinal arterioles which supplied a region temporal to the optic disc including the macula

For the 12 patients followed up table 3 shows the visual acuities on examination in the Department immediately after the onset of the occlusion and at the follow up

It is seen that the visual acuity deteriorated somewhat during the observation period (on an average 8 0 years) Thus two patients with perception of light immediately after the occlusion had no light perception of this eye at the follow up

Motility and position Of the 12 patients followed up three had secondary divergent strabismus of the affected eye at the time of the follow up All three

Table 2

Visual acuity of the affected eye immediately after the occlusion in 25 patients with occlusion of the central retinal artery deceased at follow up

– L	5
+ L	5
hand movem	7
finger count	5
< 6/60	1
6/12	1
unknown	1
Total	25

Table 3

Visual acuity of the affected eye immediately after the occlusion and at follow up in 12 patients with occlusion of the central retinal artery

Vision	At occlusion	At follow up
– L	2	4
+ L	3	1
hand movements	4	3
finger counting	2	4
1/24	1	
Total	12	12

eyes were without perception of light No instances of eye muscle paresis were seen at the follow up

Pupil In eight of the 12 patients the conditions of the pupils could be assessed at the follow up Two were as stated not examined by the author in person while in two other cases assessment was impossible owing to presence of *other disorders (in one hemianopsia* and *in* the other amaurosis of the other eye owing to a previous vascular disease – central vein occlusion?) In six of the eight cases in which the pupillary conditions could be assessed the pupils

were found to be round equal and of medium size In one of the remaining two cases the pupil of the affected eye was larger than that of the healthy eye (2 5 and 1 5 mm respectively) and in the other the pupillary sizes were not comparable because the other eye had been subjected to cataract extraction with full iridectomy

The pupillary reflex on exposure to light direct on the affected eye was abolished in six of the eight patients four with - L and two with finger counting In the remaining two cases the pupil of the affected eye reacted sluggishly and relatively little In these cases the vision was finger counting and hand movements respectively The indirect pupillary reflex in response to light on the other non affected eye was normal in all eight cases

The pupillary reflex of the non affected eye on exposure to direct light was normal in these eight patients The indirect pupillary reflex of this eye in response to light on the affected eye was abolished in four patients (three with - L and one with finger counting of affected eye) very sluggish in three (one with - L and two with finger counting of affected eye) and normal in one with hand movements of affected eye

Summarizing we may say that at abolished light perception of the affected eye direct pupillary reflex on exposure to light is absent This corresponds with the fact that all the afferent fibres of the pupillary reflex are interrupted as might be expected The indirect pupillary reflex of the affected eye in response to light on the other healthy eye is normal the efferent *proportion* of the pupillary reflex being intact

Intra ocular tension The intra ocular tension was measured at the follow up in ten cases in nine with applanation tonometer and *in one* with Schiøtz tonometer

One of these patients was found to have simple glaucoma of both eyes with no change of the optic disc or loss of function of the healthy eye The tension of this eye was at a slightly higher level than that of the eye affected by central artery occlusion Another had aphakia of the other eye after cataract operation while a third had previously experienced acute disease of the other eye with loss of vision (central vein occlusion?) These three patients had to be ruled out from the study aiming at elucidating whether a central artery occlusion will in the long run alter the level of the tension

Table 4 shows the intra ocular tensions of the affected and the non affected eye of seven patients with central artery occlusion

It is seen that at the follow up (on an average 8 0 years after the occlusion) the mean intra ocular tension was a little lower in the affected eye (15 0 mm Hg) than in the other eye (16 2 mm Hg) Though the series was small the result suggests that central artery occlusion causes a minor fall in tension There was no instance of hemorrhagic glaucoma after central artery occlusion in the

Table 4
Intraocular tension in mm Hg at follow up in seven patients with occlusion of the central retinal artery

	affected eye	non affected eye
	17	18
	13	15
	15	15
	13	14
	18	20
	17	17
	12	14 5
Average intra ocular tension	15 0	16 2

stated series This is in fact a rare complication being seen in less than 1 per cent of cases with central artery occlusion (*Madsen* 1965) However *Liversedge & Smith* (1962) found 4 cases of hemorrhagic glaucoma in 62 patients with occlusion of the central retinal artery

Ophthalmoscopic findings at the follow-up The ophthalmoscopic image at the acute stage of central artery occlusion the milky white retinal oedema at the posterior pole the thin sometimes hardly visible arterioles in some instances with a visible interrupted blood stream and the cherry red spot in the fovea is well known A description of this is therefore not intended in this place The acute image fades away in the course of the first 4 6 weeks and is succeeded by the long term ophthalmoscopic image which develops during the months following the onset of the occlusion The latter is rather undiversified and characterized by the following features (See fig 1)

The optic disc is well defined and moderately pale throughout The wasting away of the nervous fibres on the disc is most often indicated by a visible lamina cribrosa marking though less pronounced than in glaucomatous optic nerve atrophy The arterioles are thin often as thin as sewing thread sometimes showing whitish lateral streaks In a few instances visible arterial collaterals have been formed on and at the disc (*Jensen* 1938) The veins are abnormally thin though not so thin as the arterioles The macula display no foveal reflex and fairly often shows finely granular pigmentation Apart from the changes described the retina looks normal

At the follow up ten patients were examined by the author who made the following observations The optic disc was well defined in all cases and moderately pale throughout Five patients had a visible though weak cribrosa marking This phenomenon was absent in two cases while its presence was not noted in three

In three patients the arterioles were thin and in seven fine as sewing thread One displayed a developed arteriolar collateral The superior temporal artery was invisible on the disc and over a distance of three fourths disc diameter At this site a corkscrew like winding collateral arteriole was seen emerging at the disc margin as a cilioretinal arteriole This arteriole communicated peripherally with the superior temporal artery where this became visible again

The foveal reflex was absent in all ten cases In three a slight finely granular pigmentation was noticed in the macular region

No other retinal abnormalities were observed

Erythrocyte sedimentation rate The sedimentation rate at the onset of occlusion has been recorded for 20 of the total series of 37 patients In 14 of these it was 12 or lower In the remaining six it was 18 29 31 4[illegible] 50 and 52 Note that no cases of temporal arteritis were found in this series

Renal disorder 22 of the 25 deceased patients had had the *urine analyzed* for protein Proteinuria was found in only three of these Two of the patients with proteinuria had the blood urea measured which was found to be normal in both cases Within the group followed up urine from 10 of the 12 patients was analyzed Only one of these who also suffered from prostatic hypertrophy had proteinuria The serum creatinine level was 1 3 mg %

Cardiovascular Conditions

Blood pressure The blood pressure was recorded for 34 of the total series of 37 see table 5

The table shows that a raised systolic pressure (>1[illegible]) was measured in half (11 out of 22) of the group dead at the time of the follow up and in a scant half (5 out of 12) of the group followed up The series under review allows of no definite conclusion as to whether a raised blood pressure contributes in any way towards provoking central artery occlusion The raised blood pressure was doubtless a contributory cause of the previously mentioned excess mortality within the group of dead at the follow up compared with the normal population

Cardiac disorders Symptoms Five of the 25 who had died at the time of the follow up are known to have suffered from angina pectoris Two of these as

Table 5

Systolic blood pressure in 22 out of 25 deceased and in 12 followed up

Systolic blood pressure < *150*	*150 170*	*175 195*	> *200*	Total
22 deceased				
4	7	5	6	22
12 followed up				
3	4	4	1	12

well as two others of the same group had dyspnoea on exertion and yet another attacks of dyspnoea at night

Two patients of this group had given a history of rheumatic infection One of these (with dyspnoea on exertion) had had four attacks of St Vitus dance between the ages of 6 and 9 and experienced *right central artery occlusion* at the age of 42 This patient died at the age of 53

The other who had dyspnoea on exertion and angina pectoris had had rheumatic fever at the age of 11 12 years and experienced central artery occlusion at the age of 52 Rheumatic aortic heart disease was then diagnosed He died 57 years old

Three of the 12 followed up had angina pectoris which however in one case subsided after reducing weight

Objective signs The *electrocardiogram* is known for 14 of the 25 deceased patients and 8 of the 12 followed up It was normal in five out of 14 in the former group and in five out of eight in the latter In six of the former group the pathological electrocardiogram showed left overloading Among these were four of the five with angina pectoris (the fifth had a normal electrocardiogram) In one case auricular flutter was seen and in the remaining two changes of the S and T deflections Within the group followed up the electrocardiographic changes consisted in left overloading in two cases (both with angina pectoris No electrocardiogram recorded for the third patient with angina pectoris in this group) and right heart block in one

X-ray of heart and thorax was performed on 11 of the 25 deceased and eight of the 12 followed up In 10 of the 11 in the former group the heart vessels shadow showed pathological conditions In eight of these the heart was seen to

be increased in breadth and in four of the latter also the aorta. In one there was found aortic ectasia and arteriosclerosis and in one aortic arteriosclerosis The 11th who presented signs of a previous tuberculosis of the lungs had a normal heart vessel shadow

In the group followed up X ray showed normal conditions in two out of eight examined Five had enlarged heart and two of these also radiographic signs of pulmonary emphysema In the last one of these eight there was found aortic arteriosclerosis

Coronary occlusion was recorded in one case only but the causes of death in the group of deceased have not been inquired into

Other vascular diseases Two of the 25 deceased had had intermittent claudication In one of these X ray of the legs showed pronounced calcifications of the arteries of the left leg and in the other arteriosclerosis of both femoral arteries

One of the 12 followed up had intermittent claudication In this patient occlusion of the left femoral artery three years after the onset of occlusion of the central retinal artery led to amputation including the femur

In one patient within the group of deceased the central artery occlusion was preceded 18 months previously by a central vein occlusion in the other eye accompanied by a non adjustable glaucoma Yet another patient (in the group followed up) gave a history of loss of vision of the other eye nine years before the onset of central artery occlusion possibly owing to central vein occlusion This could not be verified however because the patient had not consulted an ophthalmologist when the loss of vision occurred and at the onset of central artery occlusion ophthalmoscopy was impossible on account of cataract Further the eye was affected with haemorrhagic glaucoma At the follow up the lens was unaltered but the tension was low (7 mm measured with applanation tonometer)

Other vascular diseases in the carotid vertebral region Six (16 per cent) of 37 patients (five within the group of deceased) had or developed contralateral neurological symptoms (mono or hemipareses hemianaesthesiae homonymous hemianopsia aphasia in some cases loss or clouding of consciousness) Such symptoms may occur before simultaneously with or after the central artery occlusion In two patients the contralateral neurological symptoms occurred before the occlusion in one as transient attacks of right hemiparesis and aphasia some – not specified – time before the left central artery occlusion and in the other as left hemiparesis two days before the central artery occlusion of the right eye

In the third patient who three days previously had been found lying confused

Table 5

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Systolic blood pressure < 150	150 170	175 195	> 200	Total
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12 followed up				
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One of the 12 followed up had intermittent claudication In this patient occlusion of the left femoral artery three years after the onset of occlusion of the central retinal artery led to amputation including the femur

In one patient within the group of deceased the central artery occlusion was preceded 18 months previously by a central vein occlusion in the other eye accompanied by a non adjustable glaucoma Yet another patient (in the group followed up) gave a history of loss of vision of the other eye nine years before the onset of central artery occlusion possibly owing to central vein occlusion This could not be verified however because the patient had not consulted an ophthalmologist when the loss of vision occurred and at the onset of central artery occlusion ophthalmoscopy was impossible on account of cataract Further the eye was affected with haemorrhagic glaucoma At the follow up the lens was unaltered but the tension was low (7 mm measured with applanation tonometer)

Other vascular diseases in the carotid vertebral region Six (16 per cent) of 3 patients (five within the group of deceased) had or developed contralateral neurological symptoms (mono or hemipareses hemianaesthesiae homonymous hemianopsia aphasia in some cases loss or clouding of consciousness) Such symptoms may occur before simultaneously with or after the central artery occlusion In two patients the contralateral neurological symptoms occurred before the occlusion in one as transient attacks of right hemiparesis and aphasia some – not specified – time before the left central artery occlusion and in the other as left hemiparesis two days before the central artery occlusion of the right eye

In the third patient who three days previously had been found lying confused

with left facial palsy and left hemiparesis an apparently fresh central artery occlusion was noticed on eye examination

For the fourth patient we have information on occurrence that same year of right hemiparesis and loss of vision of the left eye but the time relations of these events have not been noted in the case records

In the fifth patient a left central artery occlusion was followed one year later by transient pareses of the right arm and independently of these attacks of paraesthesia of the right cheek followed by speech impediment and facial tic A few attacks of transient paresis of the *left* arm were also noticed X ray of the skull (as well as aorta and crura) showed arteriosclerosis of the vessels

The sixth patient who was followed up experienced seven years after right central artery occlusion, a left homonymous hemianopsia and one year later *right* hemiparesis At this point of time a left carotid angiography revealed arteriosclerosis of the internal carotid

In yet another patient within the group followed up *right* hemiparesis and temporary aphasia occurred the year after right central artery occlusion In this case carotid angiography on the left side revealed arteriosclerotic changes

The characteristic clinical picture with ipsilateral blindness owing to central artery occlusion and contralateral neurological symptoms was in this country first described by *Sorensen* (1934) and later by *Ronne* (1934 1938) as *hemiplegia carotica* *Sorensen* (1934) supposed that thrombosis must be present in the internal carotid at the site where the ophthalmic artery branches off from this *Ronne* (1934) on the other hand believed that such a thrombosis is not always responsible because he had seen a patient presenting the stated clinical picture in whom the eye with the central artery occlusion had a large functioning cilioretinal artery This being a branch of the ophthalmic artery *Ronne* regarded obstruction of the latter at the site of its branching off from the internal carotid as unlikely *Ronne* (1934) in such cases attributed the conditions observed to changes in the internal carotid walls The fact that in four patients of the present series the neurological symptoms did not occur simultaneously with the central artery occlusion (in two before and in two after this) perhaps also suggests that thrombosis of the internal carotid with obstruction at the site of branching off of the ophthalmic artery does not in all cases explain the *hemiplegia carotica* However these arguments are completely invalidated by the observation made by *Rushede* (1957) and *Spalter* (1959) that in a large proportion of cases with internal carotid thrombosis (*Rushede* in seven of 12 cases or 58 per cent *Spalter* 60 per cent) the ophthalmic artery on the affected side is seen arteriographically to be filled *via* collaterals from the homolateral external carotid through the internal maxillary

That the arteriosclerotic vascular wall changes (with or without associated thrombosis) are not always limited to the internal carotid concerned but often occur in the opposite one too (and in other arteries) is evidenced by the fact

that two (three) patients of the present series displayed ipsilateral hemiparesis In these cases angiography showed as stated arteriosclerotic changes in the internal carotid on the side opposite to that of the central artery occlusion

Spalter (1959) found no cases of central retinal artery occlusion among 30 patients with verified thrombosis of the internal carotid In *Hollenhorst s* (1959) series occlusion of the central retinal artery or its branches was found in eight out of 86 patients with intermittent insufficiency of the internal carotid and in six out of 38 with internal carotid thrombosis Four and two of these patients respectively also had a contralateral homonymous hemianopsia *Liversedge & Smith* (1962) found 16 with neurological symptoms among 63 neuromedical examined patients out of a material of 98 patients consisting of 84 with central retinal artery occlusion and 14 with branch occlusion *Kjer & Jorgensen* (1968) saw two patients with central artery occlusion among 42 with carotid artery disease examined in a neurological unit

Comments and Conclusions

As might be expected the follow up of patients with central retinal artery oc clusion revealed a poor visual prognosis The visual acuity was in only one case better at the follow up than shortly after the onset of occlusion

Central retinal artery occlusion is a disease affecting elderly individuals The disease is rare before the age of 40 a little more frequent between the ages of 40 and 60 and most frequent in the age class of 60 80

To judge from the series under review patients with central retinal artery occlusion have a considerably shorter life time than the normal population In the group of 25 patients dead at the time of the follow up the mean life time after the onset of central retinal artery occlusion was 5.5 years against a computed life time of 15 4 years for a corresponding normal population in Denmark The poor life prognosis is doubtless due to the fact that many of these patients suffer from hypertensive and arteriosclerotic cardiovascular dis eases Eleven out of 12 patients of this group had a systolic blood pressure above 175 mm Hg and cardiac hypertensive changes were frequent The rather frequent combination of ipsilateral central retinal artery occlusion and contra lateral neurological symptoms indicative of a vascular (arteriosclerotic) disease in the carotid region on the same side is a remarkable feature among the ar teriosclerotic vascular disorders in this group The two cases with central retinal artery occlusion and ipsilateral neurological symptoms where arteriography revealed arteriosclerotic changes in the internal carotid on the side opposite to that of the occlusion showed that the disease is not a local one

with left facial palsy and left hemiparesis an apparently fresh central artery occlusion was noticed on eye examination

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Summary

A series from a 12 year period comprising 37 patients (21 males and 16 females) with central retinal artery occlusion was followed up 25 had died at the time of the follow up The mean age at the time of onset of the central artery occlusion was 63 0 The mean life time after the onset of central artery occlusion was considerably shorter for the 25 patients dead at the time of the follow up than that calculated for a corresponding normal population in Denmark (5 5 years against 15 4 years) The frequent concurrence of hypertensive arteriosclerotic, cardiovascular diseases is believed to be the cause of the poor life prognosis in this group Thus six patients (16 per cent) of the whole series plainly showed ipsilateral central retinal artery occlusion and contralateral neurological symptoms (hemiparesis hemianaesthesia homonymous hemianopsia aphasia) The visual prognosis was poor for all the 12 patients followed up In seven of these the mean intra ocular tension of the affected eye was 1 2 mm Hg lower than that of the healthy eye The late ophthalmoscopic image of the central retinal artery occlusion was characterized uniformly by diffuse optic disc atrophy thin to sewing thread fine arterioles and absent foveal reflex Three of the 12 followed up showed a secondary divergent strabismus of the affected eye

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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TENUITY OF CORNEA WITH EHLERS-DANLOS SYNDROME

BY

B MOESTRUP

Ehlers Danlos syndrome is a hereditary mesodermal dysplasia which in complete cases is characterized by hyperelasticity of the skin hyperextensibility of the joints and fragility of the skin and the blood vessels To these main symptoms can be added the abnormal posttraumatic scarring and molluscoid pseudo tumors Various deformities have been described in patients with the syndrome e g pes planus kyphoscoliosis[1] pectus excavatum[2,3] pectus carinatum[4] and arachnodactylia[7] Herniae are frequent often congenital e g inguinal herniae or umbilical herniae[1,4,5] Internal organs may likewise show manifestations Thus several cases of dissecting aorta aneurysms have been described[1,6] Heredity is autosomal dominant yet showing variable penetrance[7,8]

The ophthalmological interest in Ehlers Danlos syndrome originates in a series of eye symptoms described in patients with the syndrome Yet none of the eye symptoms occur with a constancy or a regularity sufficient to making them really characteristic of the syndrome Epicanthus[1,3,8,9,10,11] strabismus[3,6,11,12] and hypertelorism[8,11] have been reported The upper eyelid is often easily turned through a pull of the skin the socalled Méteniers sign Blue sclerae have often been observed in patients with Ehlers Danlos syndrome[6,9,13] Durham[10] has described a patient with blue sclerae microcornea and glaucoma Thomas et al[13,14] have given descriptions of a two year old girl with bilateral keratoconus where both corneae were ruptured after inadequate trauma within a short time of each other Healing went slowly and on both sides

pronounced leucoma followed The same writers have described bilateral lens luxation in a fortyeight year old man with Ehlers Danlos syndrome[15] Cottini[12] has reported angioid streaks in a patient suffering from Ehlers Danlos syndrome as well as from Groenblad Strandbergs syndrome Green et al[3] have observed two perfect cases of Ehlers Danlos syndrome with angioid streaks Pemberton et al[6] have scrutinized three generations of a family six out of seven members of which suffered from myopia and amotio retinae Four of these had symptoms indicating Ehlers Danlos syndrome Bossu and Lambrechts[8] have reported a case a nineteen year old girl where one side showed degeneration of macula and the other side retinitis proliferans with secondary amotio Myopia has been reported by several writers[6, 9, 10, 11]

Report of a case

3 10/12 year old girl Anamnestically it was informed that the girl often fell and easily caught hematomae Her skin had always been *thin* delicate and fragile About two hours before the hospitalisation the child had got a slight stroke on the left cheek The eye region had not been hit Immediately after she complained of reduction of sight on her left eye

The examination revealed hypertelorism and bilateral slight ptosis There was a positive Méténier s sign
Sclera was markedly blue on both sides
Visus o dxt 3/13 — 3 0 spherical
Visus o sin light sense

Right Eye

lit lamp	cornea thin otherwise normal Iris and lens normal
ophthalmoscopy	(under narcosis) normal conditions
Javal	± 1 0 0
tension	palpatorically normal
thickness of cornea	0 98 mm
length of axis	(measured by ultra sound) 23 19 mm

Left Eye

slit lamp	cornea thin Downwards about 2 mm from limbus a 5 6 mm long concentric rupture with iris prolapse. Lens initiatorily cataractuous was subluxated with the lower

edge forward corresponding to the rupture of cornea Neither cornea palpebrae nor eye surroundings revealed signs of lesions of external origin

After section of the prolapsed *iris tissue and irrigation of the lens masses* suturing of the rupture of cornea was attempted this however proved impossible as the sutures cut through the thin fragile cornea tissue Thereafter grafting of Tenon s capsule was tried but this likewise was so thin and delicate that grafting was not possible Alternatively a free grafting of a piece of conjunctiva *taken from fornix inferior*, was made Healing went slowly The conjunctiva flap was exfoliated in the course of some ten days but not till three weeks later was cicatrix solid with strong growth of vessels The patient was discharged after four weeks of hospitalisation By the discharge safety glasses were prescribed By a control examination seven weeks later cicatrix was solid white with fewer vessels

The general examination of the patient unveiled many of the symptoms typical of Ehlers Danlos syndrome There were extensible elastic skin and hyperextensibility of all joints The skin showed remnants of hematomae in several places Besides were found arachnodactylia pes planus hernia paraumbilicalis and pectus excavatum

Ecg X-ray of thorax and cranium dental examination and audiometry showed normal conditions The secretion of amino acids in the urine was normal

Discussion

Many of the symptoms characteristic of the Ehlers Danlos syndrome can be observed as parts of other mesodermal syndromes and here as a more constant find – characteristic of the syndrome Thus blue sclerae are practically constant in osteogenesis imperfecta Lens luxation is frequent in Marfan s syndrome where it may be found in 80 85 per cent of the cases Angioid streaks is the eye find typical of Groenblad Strandbergs syndrome Thin corneae causing keratoconus have been described in Ehlers Danlos syndrome as well as in Marfan s syndrome and van der Hoeve s syndrome Bertelsen[18] has described two intimately related persons with blue sclerae and thin corneae There was no keratoconus Diameter of cornea was larger than normal Ruptures of both corneae after inadequate trauma occurred with the interval of one year in one of the patients One eye had to be enucleated *By microscopy the* thickness of cornea was found to be reduced to 0 2 mm Bowman s membrane was found strongly reduced in thickness and in substantia propria the number of lamellae

was cut down to nearly half the normal and besides the individual lamella was thinner than normal Both sclera and cornea showed far more reticular fibres than normal None of the patients might safely be grouped under any known mesodermal syndromes although osteogenesis imperfecta might not be precluded

The thin cornea in our patient may be explained as a dysgenesis of the mesodermal layers in cornea of a kind similar to the one described by Bertelsen A simultaneous weakening of zonula Zinni as a part of the general mesenchymal dystrophy may have the effect that even a slight indirect trauma will cause lens luxation and thereby start the dramatic eye symptoms

Summary

A report has been given of a case of the Ehlers Danlos syndrome in a barely four year old girl where an inadequate indirect trauma caused lens luxation and rupture of cornea on the left eye Both corneae were thin On the right eye thickness of cornea was measured to 0 28 mm Furthermore epicanthus and blue sclerae were revealed The etiology of the reduced thickness of cornea is an object of discussion

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Eye Department E
(Chief P M Møller M D)

A NEW OPHTHALMOLOGICAL EXAMINATION UNIT

BY

P M MØLLER

During the construction of the new ophthalmological department of Odense County and City Hospital we designed a new examination unit for ophthalmological patients This unit is situated in the out patient clinic of the department and is constructed with the object of covering all the examinations necessary of both out patients and hospitalized patients

It is often difficult to carry out a complete ophthalmological examination of a patient with the special instruments required because these are normally placed in such a position that it is necessary to move the patient from the one instrument to another This transport covers at times longer distances from especially constructed ophthalmoscopical units to rooms intended for perimetry only We decided when designing the unit to place the patient in the centre of the unit and positioned all the necessary instruments around the patient in such a manner that the patient can remain in the examinationchair throughout the whole examination This is of inestimable value particularly for older or debilitated patients In this way much time is saved and tiring transport of patients avoided We have worked together with the architects and engineers on this unit for several years using the trial and error method and now consider that we have obtained a unit that is satisfactory in all respects

As it appears to us that we have constructed a new and untraditional unit we would like to publish the results

Fig 1 is an overall drawing of our examination unit having an area of 36 m

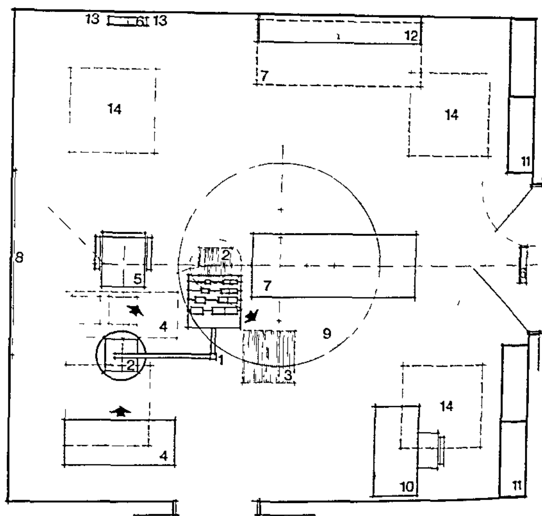


Fig 1

1 Column (revolving)
2 Visual acuity chart
3 Trial set
4 Double table
5 Patient chair (revolving)
6 Mirrors
7 Stretcher
8 Bjerrum screen (wall)
9 Bjerrum screen (ceiling)
10 Desk (Secretary)
11 Instrument cupboard
12 Instrument shelves
13 Fixation lights
14 Skylights (electr closure)

The instruments used for the examination are all placed around the patient chair (5)*) This chair can readily be turned into four previously determined positions namely towards the mirror (6) placed between the two fixation lights (13) towards the Bjerrum screen on the wall (8) towards the slit lamp and ophthalmometer table (4) and finally to a position when using the special instruments lodged on the rear of the lid of the trial set

In our opinion it is essential that the examination chair can also be raised and lowered and this is done electrically from switches on both the trial set and the double table with the slit lamp and ophthalmometer The adjustment

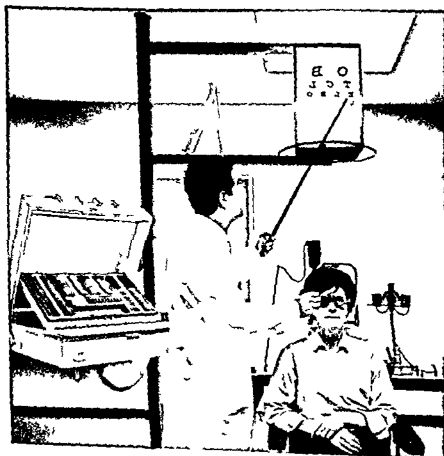


Fig II

*) All the numbers mentioned refer to Fig 1

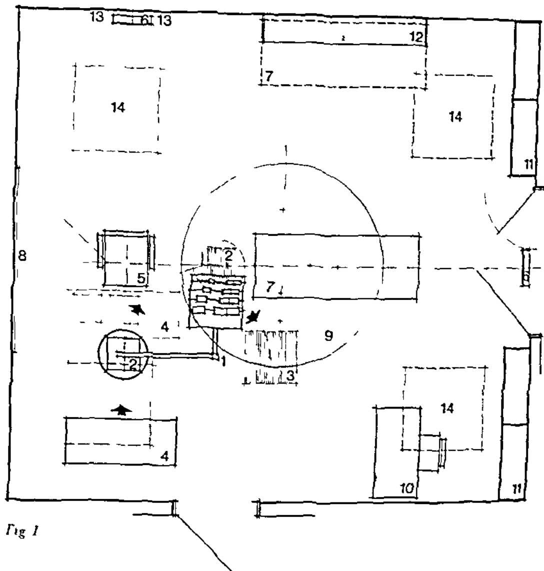


Fig 1

1 Column (revolving)
2 Visual acuity chart
3 *Trial set*
4 Double table
5 Patient chair (revolving)
6 Mirrors
7 Stretcher
8 Bjerrum screen (wall)
9 *Bjerrum screen (ceiling)*
10 Desk (Secretary)
11 Instrument cupboard
12 Instrument shelves
13 Fixation lights
14 Skylights (electr closure)

column Switches controlling the lighting in the trial set and the vision test chart of the Snellen type and those for the adjustment of the height of the examination chair are also situated on the trial set

Fig III shows the chair turned and adjusted to the correct height for examining the patient with the slit lamp and the ophthalmometer These are placed on a moveable double table (4) The positions of the hand instruments situated on the rear of the lid of the trial set can also be seen from this figure The double table (4) is pushed backward in *fig IV* and the patient looking towards the campimeter (8) The distance from the examination chair to the campimeter is one meter thus objects of varying size and colour can be projected onto the screen Switches are placed to the left of the campimeter (3) which permit adjustment of the illumination of the room complete illumination from the skylights (14) can be obtained to complete darkness for ophthalmoscopy and retinoscopy The instruments for this examination are as previously mentioned placed on the rear of the lid of the trial set The spiralwires permit complete freedom of movement with the instruments The transformer for these is situated in the base of the trial set

The lamp with a moveable arm situated on the support bearing the rotating visual test chart is intended for illuminating the hand reading chart and to

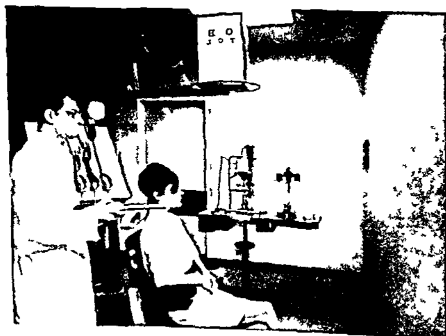


Fig II

of the patient to the correct height is thus carried out rapidly and easily for ophthalmoscopy determination of the field of vision investigation of direct vision and biomicroscopy of the eye

Fig II shows the patient placed in the correct position for the investigation of direct vision by reading from a mirror (6) the latter being placed between the fixation lights (13) The revolving column (1) is shown in this picture in the primary position bearing a visual acuity chart of the Snellen type (2) where the letters are painted on opal glass and illuminated from the rear The visual acuity chart can be turned to four positions thus allowing the size of the letters and the text To be varied the trial set (3) in the lid of which the instruments for ophthalmoscopy transillumination sciascopy and a projector for deter mination of the visual field are built in is also attached to the revolving

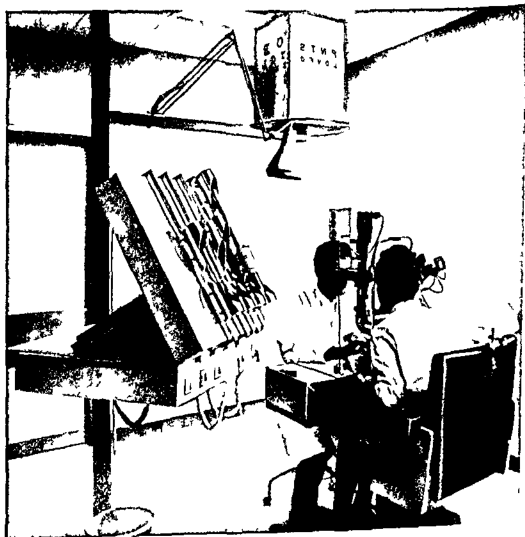


Fig III

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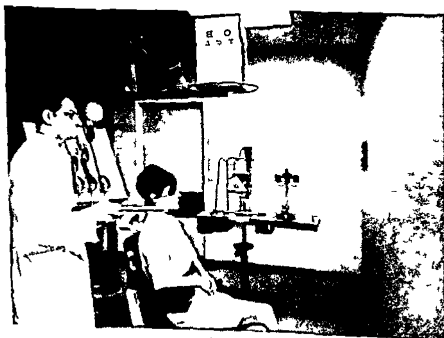


Fig IV

of the patient to the correct height is thus carried out rapidly and easily for ophthalmoscopy, determination of the field of vision investigation of direct vision and biomicroscopy of the eye

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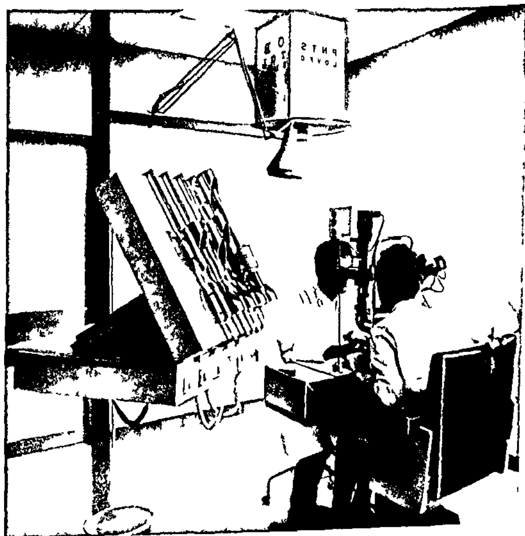


Fig III

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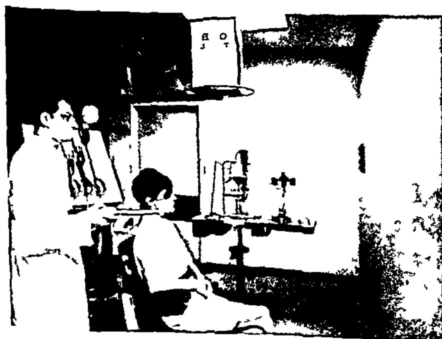


Fig IV

provide sufficient light for examining the surroundings of the eye This can also be done with the patient in the supine position in as much as the back of the chair can be lowered

Fig V shows a patient on a stretcher or bed moved into position for the examination The column is turned 90 ° and it is then possible to examine the patient with the same instruments and to test the vision using the mirror placed above the door (6) The trial set in this figure has been turned on its horizontal axis so that it is conveniently placed for taking the ophthalmoscope without moving The projector is also easily available for determination of the visual field the screen of which is attached to the ceiling (9) The distance from the screen to the patient is 1 50 meters The lamp for local illumination is also within easy reach when the patient is in the supine position

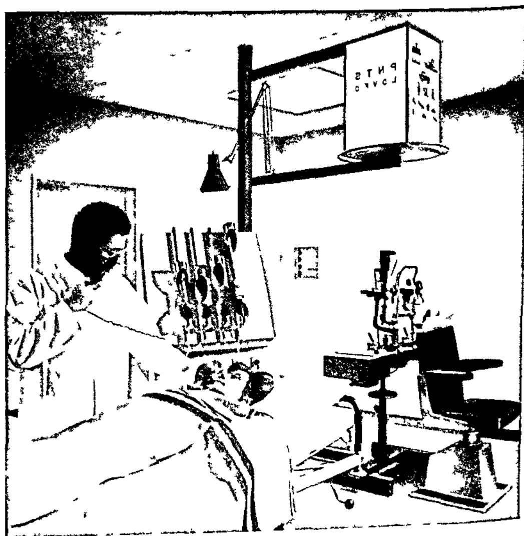


Fig V

The column can be turned 90 ° to its original position near the examination chair following examination of a patient in bed and the instruments are then ready for use if the next patient is ambulatory

I wish to thank both architect Helmuth Knudsen and engineer Johannes Vig from respectively Jørgen Stærmose & Kay Boeck Hansen and Birch & Krogboe for their inestimable help in the construction of the unit.

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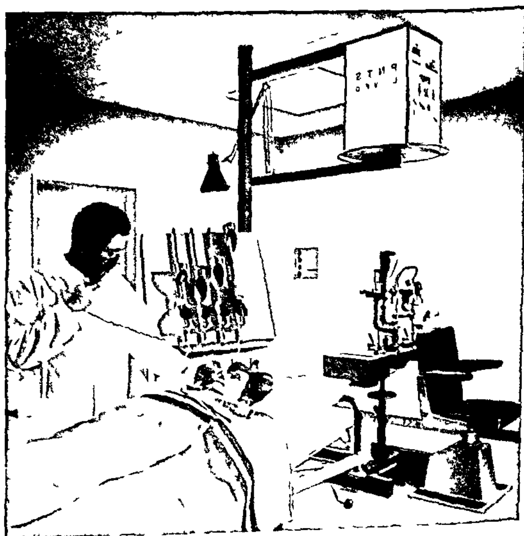


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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the Hematology Laboratory
Department of Medicine and the Department of Experimental Ophthalmology
University Hospital Lund Sweden

MEASUREMENT OF DARK ADAPTATION IN VITAMIN A DEFICIENCY BY A NEW QUANTITATIVE TECHNIQUE

BY

A NORDÉN and G STIGMAR

Vitamin A intoxication by overdosage and vitamin A deficiency due to fat malabsorption represent clinical situations in which techniques for the assessment of tissue vitamin A are highly desirable

In the present study a method has been elaborated for the quantitative determination of dark adaptation Since current chemical methods may be open to criticism a functional test related to the availability of vitamin A in the tissues appeared to represent an approach worth exploring

Technique for the measurement of dark adaptation

The apparatus used in these examinations is an automatic adaptometer designed by Krakau and Öhman (1) The light source is a photolumenescent plate The luminance of the plate depends on the voltage applied and it can be varied over a wide range by varying the current through the plate With this method neither filters nor shutters have to be employed The luminance of the plate can be logarithmically reduced in 36 steps the quotient between the light intensity at its brightest and that at its faintest being about 130 000 The course of adaptation is recorded as relative threshold values in a diagram The process of altering the luminance is regulated by the choices of the subject in the following way A random generator makes the luminescent plate illuminated or not with equal chances for light and no light The subject is instructed to

press a button when light is seen and – obviously – do nothing when no light can be perceived Thus the intervals between the periods of light are randomly varied After three consecutive and correctly interpreted choices the luminance of the test plate is automatically reduced one step (by a factor 1/1 4) If the subject cannot perceive a certain luminance (and does not press the button) or if he presses the button when no light is shown the luminance is increased one step (i e by a factor 1 4) Thus a step curve is recorded from which the relative threshold values in the course of adaptation are easily obtained

The subjects are pre adapted for a period of three minutes In this case only the central visual field was examined and eye fixation was kept steady by a dark red light The maximal exposure time inside which the patient had to make his choice to press the button was four seconds The whole procedure extended over 23 minutes Instructions to the subjects and starting of the procedure are managed by a technical assistant

Case history

The patient was a [illegible] year old unmarried women A O 46 03 07 She had had diarrhoea since early childhood and at the age of seven been treated for coeliac disease

In 1964 at the age of 18 she was found to have a bleeding tendency due to vitamin K deficiency At about the same time walking difficulties were observed

In 1966 bleeding again caused admission for investigation This could *also now be explained* by vitamin K deficiency Study of coagulation factors showed no abnormality

Further investigation demonstrated fat malabsorption with a fecal fat excretion varying between 19 and 6? g per day

Serum vitamin B_{12} and serum folate were normal Biopsy of the intestinal mucosa was normal X ray of the intestine showed no abnormality Pancreatic function was normal

She had a normal serum bilirubin of 0 6 mg* GOT and GPT were *increased* 61 and [illegible] units Serum alkaline phosphatase was normal 5 *units*

Br msulphalein clearance showed ?? per cent retention at 30 minutes and ?9 per cent at 120 minutes suggesting a Dubin Johnson syndrome

An assay of her bile production gave 0 30 0 66 mg of bile salts per ml control subjects 9 3 mg ml

Her walking difficulties were diagnosed as a combined myopathy and neuropathy Assay for plasma vitamin E showed 0 15 mg of tocopherol per 100 ml (Normal control [illegible] mg per 100 ml)

Her myopathy neuropathy was assumed to be related *to deficiency* of vitamin E. The patient was thus diagnosed as a *case of fat* malabsorption with secondary deficiency of the fat soluble vitamins K and E The *primary cause* for the malabsorption was assumed to be deficient bile acid production.

This prompted studies of the absorption of *vitamin A*

Eye examination

The unaided visual acuity was 1 0 There was an intermittent exotropia Findings of *external slit lamp* visual field and colour vision examinations were normal Ophthalmoscopy revealed no signs of pigmentary degeneration of the retina

Dark adaptation and response to treatment

The patient had only a vague sense of hemeralopia but the dark adaptation curve on time of admission was elevated in the scotopic range with an abnormally high threshold after a 20 minute period of adaptation (fig 1) After oral *treatment* with 3000 I U vitamin A in colloidal water suspension daily the dark adaptation was normalized (fig 2) but when the treatment was reduced to half that dose the adaptation curve was impaired Obviously a daily treatment of 1500 I U was not enough to maintain a normal adaptation level The examinations were repeated and there was always a close connection between the given dose of vitamin A and the threshold values (fig 3) When treatment with 1500 daily I U was instituted the effect of one single dose of 3000 I U could be studied This higher dose was given orally at 9 a m 2 hours later there was no significant response on the dark adaptation but after 4 hours a clear improvement was recorded and normal values were obtained 6 hours after the medication Due to the rapid detoriation of the dark adaptation when the daily dose of vitamin A was reduced it was possible to repeat the examinations The results were found to be reproduceable

Some modifications of the treatment have been made The vitamin A was administrated in a solution of peanut oil but it was not possible to record any significant improvement of the dark adaptation When vitamin A was omitted for vitamin E (200 mg vitamin E orally/day for 3 weeks followed by 500 mg

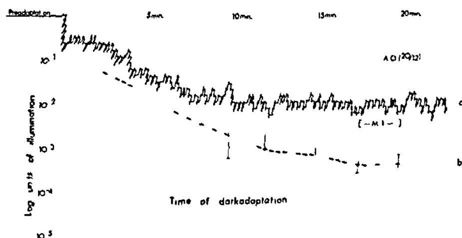


Fig 1

Dark adaptation curve on time of admission (a) in comparison with an average adaptometry curve in this age group (b)

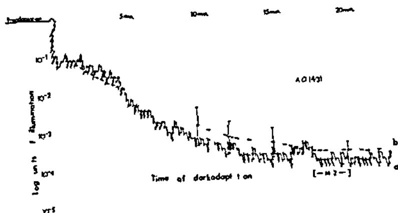


Fig 2
Dark adaptation curve after treatment with 3000 I U water soluble vitamin A (a) in comparison with an average adaptometry curve in this age group (b)

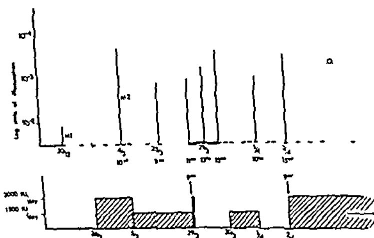


Fig 3
S me of the dark adaptation threshold levels (mean of ?.5 min in the period 17 5 0 m n) in relation to the dose of vitamin A

vitamin E parenterally/day for 3 weeks) the effect on adaption was also negative

With the purpose of giving the patient a treatment of prolonged duration the effect of parenteral therapy by a depot medicament was studied as the last on the list of investigations in this case The patient received 300 000 units vitamin A

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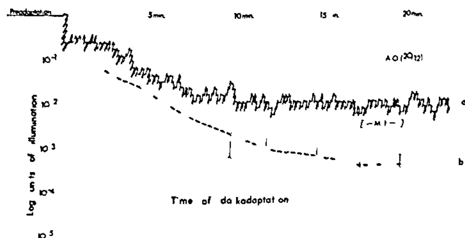


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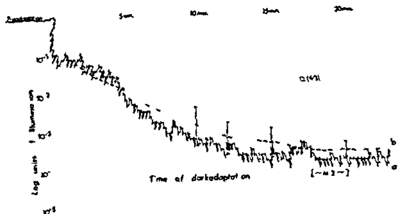


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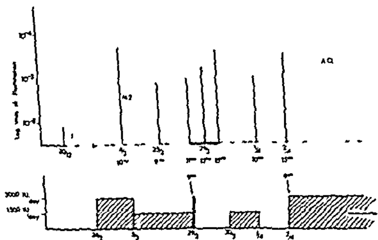


Fig 3
Some of the dark adaptation threshold levels (mean of 2.5 min in the period (15 0 min) in relation to the dose of vitamin A

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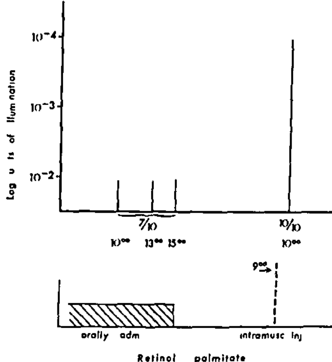


Fig 4

The 20 min adaptation level is not influenced by fat soluble vitamin A (3000 I U/day) orally adminstrated but one hour after the intramuscular injection (300 000 I U) it is normalized

(Arovit® Roche) by intramuscular injection The adaptation level was previously tested and was found to be significantly deteriorated with the same non watersoluble preparation (retinol palmitate in peanut oil) in a daily dose responding to 3000 I U vitamin A orally administrated (fig 4) The effect on the adaptation was dramatic After one hour the curve was entirely normalized and the twenty minute adaptation level was found to be improved 125 times

Discussion

In this case the dark adaptation curve was found to be a sensitive indicator of the absorbed amount of vitamin A from the alimentary tract A sub normal adaptation is frequently found associated with chronic disorders of the digestive tract but the reports on the adaptometric responses to treatment are contradictory (2 3) at least from the individual point of view It may be due to many factors influencing the absorption and utilization of vitamin A and carotene The clearcut adaptometric responses in this case must be due to a small meta

bolic pool of the vitamin A and the restricted treatment in order to limit the uptake in the liver and other tissues

In this study a certain accumulation of the vitamin was found when the patient was treated with a daily dose of 3000 I U during a period of a few weeks Half that dose was not enough to maintain the normal adaptation level Her requirement of vitamin A medication must be of about the same order as is accepted as normal for healthy individuals (about 2500 I U daily) suggesting no or only low absorption of the vitamin A content of her food The rate of absorption when orally given was indirectly indicated by the improvement of the dark adaptation curve The effect on the adaptation thresholds was noticed after 4 hours and full improvement was obtained after 6 hours This agrees well with earlier studies on the absorption of vitamin A and the rise of plasma level With parenteral administration complete restoration was achieved within one hour after the intramuscular injection

A high adaptometric threshold in a case with malabsorption may not be caused exclusively by a defective uptake of vitamin A In several recent reports the synergistic relationship between vitamins A and F has been demonstrated (for ref see 4) The sparing effect on vitamin A and carotenoids by vitamin F has been studied experimentally After the adaptation had been normalized by vitamin A the medication was changed to vitamin F injections only There was an increase in thresholds quite comparable to those found in the patient when untreated

A poor adaptometric response was also found as expected when the vitamin A alcohol was substituted by a solution of the vitamin in peanut oil Even when the dose was increased to 6000 I U no significant improvement could be recorded

When interpreting the dark adaptation responses in cases with vitamin A deficiencies one has to consider some facts which may interfere with the result of vitamin A therapy A congenital hemeralopia not apparent to the patient may be present A raised resistance to *vitamin A*", *suggested* in some reports (5) may perhaps explain an incomplete response after *treatment* A prolonged deficiency of vitamin A may cause a permanent degeneration of the retina in experimental animals (6) and this *might possibly* be the case also in man although ophthalmoscopically invisible No signs of that were found in the present case

Acknowledgement

The investigation described in this paper was supported by the Delegation for Applied Medical Defence Research of the *Swedish Ministry* of Defence and by grant No B 65 19x 1x 03 from the Swedish Medical Research Council

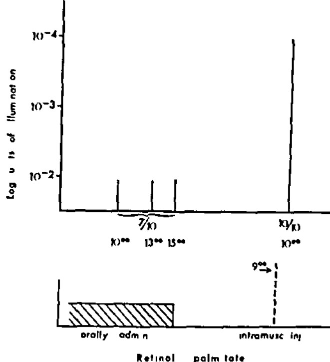


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5 *Moore T* Systemic Action of Vitamin A Exp Eye Res *3* (1964) 357 364
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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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BIREFRIGENCE OF MUCOUS FIBRILS IN THE MUCOUS THREAD OF THE INFERIOR CONJUNCTIVAL FORNIX

Polarisation Microscopy

BY

M S Norn

The Danish investigator *Erasmus Bartholinus* was the first to point out the phenomenon of double refraction (Birefrigence) The 300 years old treatise was reprinted in 1959 (Brandt)

A bundle of rays passing through a doubly refracting crystal divides into two bundles having different velocities and directions The rays consist of polarized light i e the vibration takes place in one plane only The vibration planes of the two bundles are very nearly at right angles to each other (*Pinne et al*)

By shaping the doubly refracting crystal in a special manner it is possible to make only one polarized ray pass through the crystal while the other is totally reflected and absorbed in the external part of the crystal which is ground and blackened This is the principle of the Nicol prism

Polarizing elements in a histological specimen are recognizable in a polarisation microscope

The polarisation microscope has two Nicol prisms inserted one in the part

Aided by a grant from *Kommunehospitalets 100 Års Jubilæumsfond*

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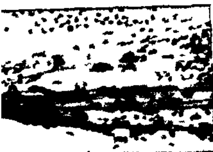
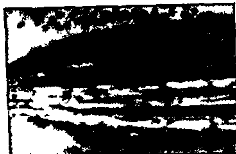



Fig 1

Section of mucous thread from the inferior conjunctival fornix of a woman aged 60 with acute infectious conjunctivitis

Mainly orthochromatic mucous fibrils Many neutrophilic leucocytes Pro fixx spray fixed stained with toluidine blue. Magnificed × 100

Fig 2

Same specimen as in fig 1 examined in polarized light All the mucous fibrils showed reddish polarisation. The nuclei of the neutrophilic leucocytes did not polarize Magnified × 100

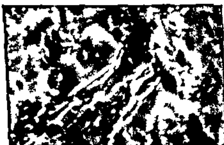



Fig 3

Part of mucous thread from the inferior conjunctival fornix of a woman aged [illegible] with chronic infectious conjunctivitis

Scattered mucous fibrils the majority showing red polarisation a small number green. Weak polarisation of nuclei of neutrophilic leucocytes Amino acridine fixed toluidine blue stained Magnified × 100 polarisation microscope

Fig 4

Vacuole in mucous thread from the inferior conjunctival fornix of a woman aged 3[illegible] with normal conjunctiva

Amino acridine fixed toluidine blue stained Magnified × 100

of rays just below the specimen named polarizer and the other in the ocular named analyzer (*Laves et al*)

The polarizer effects that only polarized light reaches the specimen If the analyzer is placed at right angles to the polarizer the field of vision will be totally darkened because the polarized ray will be retained in the analyzer

Any doubly refractive element that might be present in the specimen will divert the polarized ray The element will therefore shine brightly with the rest of the specimen as a dark background

If the polarizer is turned away from the position at right angles to the analyzer the whole specimen will shine brightly The site of the polarizing element in relation to the remaining specimen can thereby be established

Double refraction in crystals is due to the regular structure of the crystal molecules

Polarisation microscopy is mainly employed for detecting crystalline foreign bodies in tissue

Pathological tissue elements may also polarize For instance Congo red dyed amyloid shows green polarisation

Certain normal tissue elements among which fat and chromatin in some cells may likewise polarize

Various fibrous structures have been seen to polarize Collagen (*François et al*) elastic fibrils reticulin fibres neurofibrils gliafibrils smooth and striate muscles hair silk threads

The polarisation of elastic fibres increases on tightening of the fibre and decreases on slackening (*Schmidt*)

The conjunctival mucus is produced in the goblet cells of the conjunctiva from which it is liberated as fibres floating in the conjunctival fluid finally to accumulate to form a long thread in the inferior conjunctival fornix (*Norn* 1968 A)

The mucous thread in the inferior conjunctival fornix may be regarded as a band conveyor picking up foreign bodies that have entered through the palpebral fissure

The primary object of the present study was to search for polarizing foreign bodies in the mucous thread because this was supposed to give a better quantitative expression of the incidence of foreign bodies in the mucous thread Several categories of foreign bodies are probably not recognized by ordinary microscopy

The investigation disclosed however that in many cases even some of the mucous fibrils were found to polarize This phenomenon seems not to have been studied before

The mucous thread in the inferior conjunctival fornix is particularly suitable for such a study because a larger specimen of mucus is obtainable by this technique than by any other (*Norn* 1968 A)

Procedure

The limpid and therefore invisible mucous thread becomes visible by leaving some graphite granules in the inferior conjunctival fornix. These particles do not polarize and are easily recognizable in the microscope.

The patient is requested to blink a few times. This will make the graphite particles be caught by the mucous thread which can now be transferred to a glass slide between two wooden sticks. The thread is placed approximately parallel with the longest border of the slide.

The specimen is fixed immediately and subsequently stained. Different fixatives have been used (amino acridine, glutaric aldehyde, pro fixx®, air fixation, Table II).

Prior to microscopy the polarisation is controlled in a previously examined polarizing mucous thread specimen, where the thread axis parallel to the longitudinal direction of the glass slide.

Following ordinary microscopy (fig 1) the polarizer is adjusted to darkness. Maximum light intensity is provided and the polarisation is studied (fig 2).

If the polarisation is not at a maximum for the specimen concerned, the position of the analyzer is altered until maximum polarisation is obtained.

The fresh mucous thread specimen is examined with the analyzer in the same position.

The polarizing fibrillar areas are measured by means of a net ocular and are related to the *total* area of mucus measured by ordinary microscopy.

The specimens were studied in a Wild microscope with polarisation mounting at magnification × 400 (analyzer SZ 8160, compensator SZ 8161).

Polarisation of Mucous Fibrils

Non-Stained Mucous Thread

Preliminary examinations of non stained, fixed or unfixed mucous threads disclosed no polarisation of the mucous fibrils themselves (10 specimens).

A Toluidin blue stained mucous thread may lose its colour in the course of some months. The polarisation phenomenon was seen to decrease parallel with fading of the mucous fibrils.

Stained Mucous Thread

6 mucous threads were stained with different histological dye-stuffs (haematoxylin eosin, v. Gieson, Hansen, Giemsa, Unna Tass pheim, alcian blue, PAS etc).



Fig 5

Same specimen as in fig 4 examined in polarized light White polarizing foreign bodies were seen in the vacuole Such would hardly have been recognized in ordinary light A few mucous fibrils over the vacuole showed red polarisation



Fig 6

Filiform foreign body in mucous thread from the inferior conjunctival fornix of a man aged 46 with normal conjunctiva

Crumpled up white polarizing thread a few red polarizing mucous fibrils

Amino acridine fixed toluidine blue stained magnified × 100



Fig 7

Starch grains in mucous thread from the inferior conjunctival fornix of a woman aged 3 Cronic infectious conjunctivitis

Pro fixx spray fixed toluidin blue stained magnified × 250 polarisationmicroscope

The polarizing fibrils were found scattered irregularly among the non polarizing mucous fibrils They had a distinct fibrous structure also in the specimens where the mucous fibrils otherwise were blurred poorly fixed

The polarizing fibrils seemed to be continuous with non polarizing mucous fibrils

In a few specimens the double refraction included most of the mucous fibrils in one even all the fibrils (acute infectious conjunctivitis mucous area 0 6 mm fig 2)

Hence there is hardly any doubt that the polarisation phenomenon is related to the mucous fibril itself and not to occurrence of fibrin or other fibrous structures for instance such being only present in relatively small amounts in the mucous thread

Dichroism

By dichroism is understood the phenomenon that polarisation elicits different colours for the two directions of vibration Polarisation in the conjunctival mucous fibrils showed red green dichroism

By the chosen procedure with the mucous thread placed as far as possible lengthwise on the glass slide and with the chosen position of the analyzer the great majority of the longitudinally running fibrils showed red polarisation while those running transversely parallel with the short side of the slide showed green polarisation

A 90 rotation of the analyzer gave a similar interchange of red and green polarisation but with the longitudinal fibrils green and the transverse fibrils red

When the specimen was rotated 90° on the cross table the red polarizing fibrils turned green and the green polarizing fibrils red

The procedure employed gave most red polarizing fibrils In no more than 1 out of 166 mucous threads was green polarisation seen too indicating a winding course of the mucous thread or owing to presence of transverse mucous fibrils in addition to those running longitudinally (fig 3)

Metachromasia

A previous study showed that the mucous fibrils most often are *metachromatic* i e stained violet by toluidine blue more rarely orthochromatic i e stained blue (Norn 1968 A)

The polarisation colour proved to be independent of the colour of the mucous thread in non polarized light red polarisation having been seen in both orthochromatic and metachromatic fibrils

The polarizing properties thus predominate over the dye absorption properties

Polarizing mucous fibrils were found in seven specimens only, and even in very small numbers. These specimens had been stained with alcian blue or eosin.

Toluidine Blue Stained Mucous Thread

The polarisation phenomenon was much more frequent after staining with toluidine blue.

An aqueous 1 % toluidine blue solution was used for 10 minutes – more rarely 20 minutes if the colour after 10 minutes was too pale.

A total of 198 mucous threads from 198 conjunctivae of 190 patients were examined. The material is identical with that of *Norn* 1968 A and B. The clinical diagnoses have been tabulated in table I.

In most of the mucous threads (84 per cent) few mucous fibril like formations were seen which displayed intense polarisation. They constituted on an average 5 per cent of the entire mucous area.

Table I

Incidence of polarizing mucous fibrils in the mucous thread of the inferior conjunctival fornix in different clinical states

	Polarizing area aver. percentage of whole mucous thread	No polarisation number of patients	Total number of patients
normal	3	14	76
acute infectious conjunctivitis	16	3	25
subac. chron. infectious conjunctivitis	4	1	23
allergic conjunctivitis	1	4	20
blepharoconjunctivitis	2	4	14
chron. simple conjunctivitis	2	3	11
keratoconjunctivitis sicca	10	1	9
keratitis	1	0	5
epiphora	6	0	4
cataract extraction	1	1	4
sundry	3	1	7
Total	5	32	198
neutrophilia of mucous thread	14	3	42
no neutrophilia	3	29	156

The polarizing fibrils were found scattered irregularly among the non polarizing mucous fibrils They had a distinct fibrous structure also in the specimens where the mucous fibrils otherwise were blurred poorly fixed

The polarizing fibrils seemed to be continuous with non polarizing mucous fibrils

In a few specimens the double refraction included most of the mucous fibrils in one even all the fibrils (acute infectious conjunctivitis mucous area 5 6 mm² fig 2)

Hence there is hardly any doubt that the polarisation phenomenon is related to the mucous fibril itself and not to occurrence of fibrin or other fibrous structures for instance such being only present in relatively small amounts in the mucous thread

Dichroism

By dichroism is understood the phenomenon that polarisation elicits different colours for the two directions of vibration Polarisation in the conjunctival mucous fibrils showed red green dichroism.

By the chosen procedure with the mucous thread placed as far as possible lengthwise on the glass slide and with the chosen position of the analyzer the great majority of the longitudinally running fibrils showed red polarisation while those running transversely parallel with the short side of the slide showed green polarisation

A 90° rotation of the analyzer gave a similar interchange of red and green polarisation but with the longitudinal fibrils green and the transverse fibrils red

When the specimen was rotated 90° on the cross table the red polarizing fibrils turned green and the green polarizing fibrils red

The procedure employed gave most red polarizing fibrils In no more than 17 out of 166 mucous threads was green polarisation seen too indicating a winding course of the mucous thread or owing to presence of transverse mucous fibrils in addition to those running longitudinally (fig 3)

Metachromasia

A previous study showed that the mucous fibrils most often are metachromatic i e stained violet by toluidine blue more rarely orthochromatic i e stained blue (Norn 1968 A)

The polarisation colour proved to be independent of the colour of the mucous thread in non polarized light red polarisation having been seen in both ortho chromatic and metachromatic fibrils

The polarizing properties thus predominate over the dye absorption pro perties

Polarizing mucous fibrils were found in seven specimens only and even in very small numbers These specimens had been stained with alcian blue or eosin

Toluidine Blue Stained Mucous Thread

The polarisation phenomenon was much more frequent after staining with toluidine blue

An aqueous 1 % toluidine blue solution was used for 10 minutes – more rarely 20 minutes if the colour after 10 minutes was too pale

A total of 198 mucous threads from 198 conjunctivae of 190 patients were examined The material is identical with that of *Norn* 1968 A and B The clinical diagnoses have been tabulated in table I

In most of the mucous threads (84 per cent) few mucous fibril like formations were seen which displayed intense polarisation They constituted on an average 5 per cent of the entire mucous area

Table I

Incidence of polarizing mucous fibrils in the mucous thread of the inferior conjunctival fornix in different clinical states

	Polarizing area aver percentage of whole mucous thread	No polarisation number of patients	Total number of patients
normal	5	14	76
acute infectious conjunctivitis	16	3	25
subac chron infectious conjunctivitis	4	1	23
allergic conjunctivitis	1	4	20
blepharoconjunctivitis	2	4	14
chron simple conjunctivitis	2	8	11
keratoconjunctivitis sicca	10	1	9
keratitis	1	0	5
epiphora	6	0	4
cataract extraction	1	1	4
sundry	3	1	7
Total	5	32	198
neutrophilia of mucous thread	14	3	42
no neutrophilia	3	29	156

A tight linear mucous thread might be more intensely polarized than a slack crumpled up thread

A tight mucous thread is obtained by *stretching it* between two wooden sticks immediately before leaving it on the slide If the thread slips at one end or detaches itself from the glass when the fixative is placed on the slide immediately after the transfer to this the thread crumples up and becomes slack

The table shows that the phenomenon of polarisation is independent of the tension of the mucous thread

Normal Material

The polarisation phenomenon was seen in 62 out of 76 mucous threads from normal conjunctivae The polarizing mucous fibrils covered on an average 3 per cent of the total area of mucus (table I)

Age and Sex Incidence

Occurence of polarizing mucous fibrils seemed to be *independent of* age and sex (table IV) In the normal material the mean area of polarizing mucus was the smallest among women but the difference was not significant

Acute Infectious Conjunctivitis

Polarizing mucous fibrils were found in the great majority of the *mucous*

Table IV

Polarisation phenomenon in relation to sex and age

	Polarizing area aver percentage of whole mucous thread	No polarisation number of patients	Total number of patients
w men	5	11	119
men	5	21	86
under 50 years	3	12	80
0 59 years	[illegible]	4	23
60 – 63 years	6	9	51
ver 0 years	6	7	38

Fixation

The degree of polarisation seemed to be independent of the fixative used (table II)

The best fixed mucous fibrils displayed the highest degree of polarisation This fact argues against the view of the polarisation phenomenon as an arte fact The difference is not statistically significant however

Tension of the Mucous Thread

In 104 cases the tension of the mucous thread on the slide was related to the degree of polarisation (Table III)

Table II

Incidence of polarizing mucous fibrils in relation to result of fixation and fixative used A total of 124 patients

	Pro fixx spray®	Amino acridine	Glutaric aldehyde	Air fixat	Well fixed	Mode rately fixed	Poorly fixed
pol area aver per centage	6	5	0 2	4	7	6	1
(no of pts)	4	9	2	3	2	5	11
total number of pts	38	63	12	11	57	26	41

Table III

Incidence of polarizing mucous fibrils in relation to degree of tension of the mucous thread A total of 104 specimens

	Polarizing area aver percentage of whole mucous thread	No polarisation number of patients	Total number of patients
extended tight mucous thread	7	10	52
slack crumpled up muc thread	6	4	52

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men	5	21	86
under 50 years	3	12	80
50 59 years	[illegible]	4	23
60 69 years	6	9	51
over [illegible]0 years	6	7	33

threads from patients with this disease (22 out of 25) In these cases the polarizing fibrils constituted on an average 16 per cent of the mucous thread The difference from the normal material was significant (P about 0 05) The mucus is most often orthochromatic in relation to this disease

Other Clinical States

In the other clinical states the degree of polarisation seemed to be as in normals though perhaps somewhat raised in the cases of keratoconjunctivitis sicca The material is however too small to allow of any conclusions

Neutrophilia

Occurrence of neutrophilic leucocytes in the mucous thread suggests presence of infectious bacterial conjunctivitis Neutrophilic leucocytes may however also be found in normals but generally in a smaller number

The lower limit of pathological values is judged to be about 120 – 1?00 neutrophilic leucocytes per square millimeter (*Norn* 1968 B)

The mucous thread is most often orthochromatic in cases of neutrophilia (*Norn* 1968 A)

Polarizing mucous fibrils were found in the largest number and covering the largest area in the neutrophilic mucous thread (difference in area P about 0 05)

Polarisation of Cells

Polarisation of cell nuclei was noticed in 11 per cent of the specimens The number of polarizing nuclei was very small even no more than a single nucleus in some specimens

In 11 specimens polarisation was seen of nuclei of neutrophilic leucocytes The majority of these were from cases of acute infectious conjunctivitis where neutrophilia is most frequent

10 specimens showed polarisation of nuclei in cuboid or squamous epithelial cells Most of these specimens were from normals

The phenomenon was seen in cases with a fairly high degree of polarisation of the mucous fibrils but was also noticed independently of polarisation of mucus

Foreign Bodies

Doubly refractive foreign bodies were detected in all the mucous threads also in non stained specimens often only as scattered granules or small crystals polarizing white rarely red or other colours

In 26 of the 198 mucous threads the crystals were concentrated within a few vacuole like formations fig 4 and 5 (*Norn* 1968 B)

In most cases granules and crystals were found scattered over the whole mucous thread

Threads

Large filiform formations were found in 54 per cent of all the mucous threads on an average 2 3 in each specimen

The threads showed white polarisation often with a reddish or greenish tinge These threads resembled fibres of fabric or paper (fig 6)

Hairs

Hairs of different sizes were found inside or stuck on the mucous thread in 19 per cent of the specimens Two or more hairs were often seen (maximum 10 in one specimen)

The hairs polarized intensely in different colours They originated from the cilia or elsewhere

Plant Residues

Large quadrangular or irregular flakes divided into square cell segments some of which contained nuclei were noticed in 22 per cent of all the mucous threads up to four or five plant residues in each specimen

Starch Grains

Starch like grains were seen in 10 per cent of all the specimens These were round oval or somewhat angular intensely white polarizing bodies with irregular black diagonal grooves dividing the body into four sections They ranged in size from 5 to 15 μ (fig 7)

Starch grains were found in mucous threads from twelve women and seven men a total of just over 600 in the former against a total of eight in the latter

One of the female subjects also had a large patch of powder on the cheek In many cases presence of starch grains is probably due to powdering

Sources of Error

Fixatives may crystallize This is true of 5 amino acridine for instance which forms beautiful red and green needle shaped crystals

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chromasia and polarisation are both signs of altered properties of the mucous fibrils

We do not know which factor relating neutrophilia is responsible for the regular arrangement within the mucous fibril on which the intensified double refraction of this depends (Accelerated production of mucus? Increased afflux of serum? Bacterial influence?)

Polarisation microscopy disclosed a large content of foreign bodies in the mucous thread some of which could not be seen by ordinary microscopy because they were covered by mucus or cells

The observed large content of foreign bodies proves that the mucous thread has an important function as wiper of the conjunctiva and as a band conveyor The foreign bodies end on the skin of the inner canthus where the mucus dries up to become sleepy seeds

The various threads and plant residues must originate from fabric and paper while the starch grains often come from powder

The air is full of such dust particles which stick to the moist conjunctiva and cornea

In cases of pronounced accumulation of neutrophilic leucocyte one may be in doubt as to whether mucous fibrils pass through this region or stop here. Polarisation microscopy often showed polarizing fibrils to pass this region

Polarisation microscopy can thus in many instances disclose conditions that are not detectable by ordinary microscopy

Summary

Polarisation microscopy of 198 toluidine blue stained mucous threads from the inferior conjunctival fornices of 198 eyes revealed polarizing mucous fibrils in 84 *per cent of the eyes* The polarizing area of mucus averaged 5 per cent The non stained fibril did not polarize

The toluidine blue stained mucous fibrils emitted two bundles of rays one red and one somewhat paler green polarized

The polarisation capacity seems to be independent of age sex fixative metachromasia versus orthochromasia and tension of the mucous thread

Polarisation is most pronounced in cases with a large content of neutrophilic leucocytes in the mucous thread (Acute infectious conjunctivitis)

Foreign bodies are present in all mucous threads often in the forms of threads plant residues starch *grairs* and hairs indicating the importance of

In a single specimen crystallized polarizing fixative was seen in a broad zone round the mucous thread but not inside this

Tear fluid seems not to form polarizing crystals

Graphite granules were added to the mucous thread to visualize this for the sampling These granules were easily recognized in the microscope manifesting themselves as big, black grains, which did not polarize

Fine polarizing crystals granules and threads as described above were also observed on slide and cover slip outside the area covered by the mucous thread

Threads may originate from filter paper used for wiping the slide However threads were also seen even on slides not wiped

Crystals and granules may originate from dust

The concentration of such artefacts was low, however outside the mucous thread The majority of the observed foreign bodies must therefore be supposed to have been in the mucous thread in the inferior conjunctival fornix prior to the withdrawal

Discussion

Double refraction of the conjunctival mucous fibrils seems not to have been shown previously The phenomenon was seen in most of the toluidine blue stained mucous threads However most often only small areas polarized

The phenomenon must be due to regular arrangement of the fibrils or their combination with toluidine blue

The non stained mucous fibril cannot polarize

Congo red dyed amyloid for instance displays a similar polarisation phenomenon The polarisation subsides with fading of the colour *(Ranlov)*

The polarisation of the conjunctival mucous thread is independent of the degree of tension of the thread whether tight or slack Otherwise with the elastic fibril whose polarisation increases the more the fibril is extended This goes to show that the mucous thread is not elastic but is liable to burst

The polarizing capacity of the mucous thread seems to be independent of such factors as fixation the patient s age and sex and the colour of the mucous fibril itself

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In this disease the mucous fibrils are most often orthochromatic Ortho

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HOLGER EHLERS
ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

*From the Ophthalmic Department
of the University Hospital Turku Finland
(Head Prof Irvo Oksala)*

COMPARATIVE EXPERIMENTS ON THE ATTENUATION OF ULTRASOUND IN MUSCULAR AND FAT TISSUE*)

BY

ARVO OKSALA and LEENA HÄKKINEN

In the ultrasonic diagnosis of the bulbus the attenuation of ultrasound in muscular and fat tissue has no practical importance But after beginning to examine by ultrasound pathological conditions deep in the lids and especially in the orbit (*Baum* and *Greenwood* 1960 *Vanysek* and *Preisova* 1965 *Ossoinig* 1965) the knowledge of the attenuation of ultrasound in fat and muscular tissue is a very important factor in the analysis of echograms Unfortunately our information on this phenomenon is very scarce There are no studies on this subject in ophthalmological literature There is not much information on absorption in any other kind of literature either and if there is any it mainly applies to lower frequencies In addition to that the investigations have usually been made in such circumstances as very poorly correspond to the conditions at ophthalmological examinations

According to *Pohlman* (1939) the absorption coefficient of fat tissue at the frequency of 800 kc is two times lower than that of muscular tissue *Guttner* s (1954) absorption coefficient of fat tissue (2α [m⁻¹]) at the frequency of 900 kc is 0 09 and that of muscular tissue 0 26 The corresponding acoustic impedance are 1 36 and 1 63 (ρ v 10⁵ *g/cm s*) With the exception of osseous tissue the absorption coefficient in biological tissue grows linearly with the frequency According to *Goldman* and *Hueter* (1956) the absorption of muscular tissue is higher than that of fat tissue within the frequency range 400 kc – 4 Mc

*) This work was supported by a grant from the Sigrid Juselius Foundation.

the mucous thread as a means of transporting foreign bodies away from the conjunctival sac

Acknowledgement

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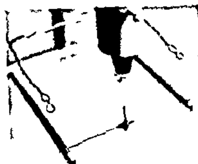


Fig 1
A plastic vessel fixed to the end of the transducer and filled with the substance that is being examined The steel ball can be seen beneath it

tissue After the axial echogram of a normal pig eye had been examined by A and B scans with the transducer at a distance of 10 mm from the cornea the fat plate was placed in the anterior chamber and the same examinations repeated These examinations were made on five different eyes

3 The influence of muscular and fat tissue on the echograms obtained from a piece of steel was studied A piece of steel was placed beneath the transducer at a distance of 15 mm By placing a 4 mm thick piece of muscular and fat tissue at 5 mm s distance from the transducer we were able to see the changes they caused on the echograms The fat tissue was taken from subcutaneous fat while the muscular tissue was from the orbit i e eye muscle tissue Five experiments were made on this material

4 We wanted to find out what an echogram reflected by muscular or fat tissue really looks like For this purpose we cut a 9 mm thick piece of sub cutaneous fat and outer eye muscle The echograms were obtained by placing the tissues at 10 mm s distance from the transducer Examinations were carried out on 5 different muscle and the same amount of fat tissue pieces

Results

1 Fig 2 shows the attenuation of ultrasound caused by water muscle or fat (the intermediate substance being in a plastic vessel) The results are given in relative figures the starting point = 100 is the amplitude of echo in water at a distance of 10 mm from the transducer The curves declining from left

In this study we have examined the attenuation of ultrasound in water, as well as muscular and fat tissue Besides actual absorption attenuation has also been caused by *reflection refraction and scattering*

Equipments, Material and Methods of Research

In our investigation we used *Kretztechnik's* ultrasound equipment, model 7000 with which we had connected a Tektronix oscilloscope 515 A for a more accurate measurement of the amplitudes of echoes The transducer was a 6 Mc/5 mm one At B scan examinations we used *Kretztechnik's* equipment *7900 S and a focused transducer of 8 Mc/5* mm

In measuring the attenuation we used a set of instruments that produced from any particular area of the sound field curves representing the relative sound pressure The transducer was fixed to a stand and a steel ball (diameter 1 5 mm) was then moved beneath the transducer and past its center The *movements of the ball could be measured at a 0 1 mm accuracy in both* horizontal and vertical directions On the basis of the amplitudes of the echoes reflected by the ball we were able to draw the curves being proportional to the relative sound pressures As water fat and muscular tissues were successively placed between the transducer and the steel ball it was possible to make comparisons between attenuations caused by different intermediate substances The reproduction and repetition of the experiments was very easy and exact

Our research material consisted of pig eyes the muscular and fat tissue of pig s orbit and pig s subcutaneous fat tissue The examinations took place 8 hours after slaughtering in a temperature of +20°C In the meantime the eyes were kept in a refrigerator (+4°C)

Comparative experiments on attenuation between the various intermediate substances were carried out in several ways

1 First a plastic vessel was attached to the end of the transducer (Fig 1) This part was successively filled with water orbital muscle tissue and orbital fat Then the echo amplitudes was measured at the distance of 10 15 and 20 mm from the transducer Ten different samples were taken of each substance which gave us a total *of 90 measurements The thickness* of the tissues was 3 mm Special attention was paid to the fact that there were no air bubbles and that the position of the plastic part was always the same The water in the experiments was freshly boiled

2 The influence of a thin plate of fat in the anterior chamber on the axial echogram of pig eye was investigated A piece 1 5 mm thick and of approximately the size of the cornea was cut out of pig s subcutaneous fat

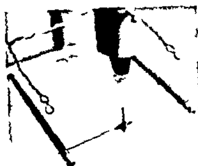


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4 We wanted to find out what an echogram reflected by muscular or fat tissue really looks like For this purpose we cut a 9 mm thick piece of sub cutaneous fat and outer eye muscle The echograms were obtained by placing the tissues at 10 mm s distance from the transducer Examinations were carried out on 5 different muscle and the same amount of fat tissue pieces

Results

1 Fig shows the attenuation of ultrasound caused by water muscle or fat the intermediate substance being in a plastic vessel) The results are given in relative figures the starting point = 100 is the amplitude of echo in water at a distance of 10 mm from the transducer The curves declining from left

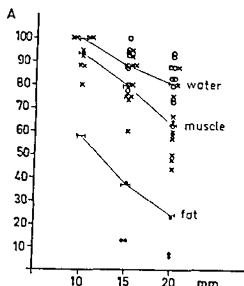


Fig 2

The highest amplitudes of echo amplitude curves at three different distances when the substance between the transducer and the steel ball was water (O) muscle (\) and fat tissue (●) The curves declining from left to right represent the means of the highest amplitudes

to right represent the means of the highest amplitudes obtained with water muscular and fat tissue at various distances

The results show that with the exception of two measurements the echo amplitude fell with an increase in the distance When we compared the attenuation of muscle with that of water we found it to be the same in 8 cases out of 30 and in another 8 cases the difference was less than 10%. The attenuation in fat tissue was definitely greater than that of water in all measurements and in 29 out of 30 cases also distinctly greater than that in muscle

Methods 2–4 yielded consistent results of which the following figures are typical examples

2 In fig 3 one can see the effect of fat tissue on the axial echogram of the eye examined by A scan Fig 3 A shows a normal echogram On the left we have the transmitter pulse followed by a zero line from the water The next high echo is reflected by the cornea The high echo that is partly connected with it corresponds to the anterior surface of the lens The echo of the posterior surface of the lens lies in the center of the echogram and the two echo peaks on the right are reflected by the rear eye wall In Fig 3 B one can see the effect of fat tissue The echoes from the posterior surface of the lens and the rear eye wall have clearly become lower The amplification



Fig 3
In A a normal axial echogram of a pig eye In B the fat in the anterior chamber has lowered the echoes of the posterior surface of the lens and the rear eye wall



Fig 4
A represents a normal pig eye examined by B scan while in B the fat in the anterior chamber throws a shadow on the echoes of the rear eye wall which will thus become weaker

of the equipment was the same in both cases a db reserve = 10 Fig 4 represents results obtained by B scan In 4 A we have the normal echogram while in 4 B the 1 5 mm thick piece of fat tissue in the anterior chamber throws a clear shadow on the echogram of the rear wall

3 Fig 5 is an example of echograms that were obtained when we studied the effects of muscular and fat tissue on echoes reflected by iron On the left in figure 5 A we have a transmitter pulse followed by a zero line representing water and on the right the echoes from a piece of iron Fig 5 B shows the results when a 4 mm thick piece of muscle tissue was placed beneath the transducer there was a slight fall in amplitudes on the echogram of the metal as compared with that of the former experiment (Fig 5 A) In Fig 5 C the



Fig 5
The echograms of iron with (A) water (B) muscle and (C) fat tissue between the transducer and the piece of iron



Fig 6
The echograms of (A) muscular and (B) fat tissue obtained in the same conditions as those in Fig 5

situation is the same with fat tissue as the intermediate substance Now we can see a very clear fall in amplitudes

4 Fig 6 A shows the echogram of muscular tissue and 6 B that of fat tissue One may notice that even in such a short distance the attenuation of ultrasound is considerably higher in fat than in muscle tissue

In order to clarify the sound loss in border surfaces water/muscle and water/fat the influence of very thin layers of tissues on the echo amplitudes was investigated No difference of sound loss was found in these border surfaces

Discussion

Fig 2 shows that the attenuation of ultrasound is pretty much the same in water and muscular tissue but in fat it is distinctly higher In the same picture one can make the observation that there are differences within the various

examinations These are partly caused bv the fact that there may have been slight differences in the thickness of tissue pieces and partly by possible changes in spite of all care in the position of the plastic part in respect to the transducer The differences did not however ever work to the effect that the attenuation in muscle would have been higher than that in fat

As the difference in attenuation between water and muscle tissue was not great we investigated the change caused by fat on the echogram of the eye As one can see in figures 3 and 4 fat tissue weakens very strongly the amplitudes of echoes According to these results an even layer of fat 1 5 mm thick would already make the diagnosis of intraocular tumors quite uncertain

The third method we used could also prove very clearly the different effects of fat and muscle tissue on the sound field A 4 mm thick piece of muscle lowered the echoes of a piece iron scarcely noticeably while at each examination the effect of a 4 mm thick piece of fat was strong The above mentioned results and the conclusions made of them are further reinforced by the great differences that were found when the echograms of muscle and fat tissue were compared with each other

The results point to the fact that muscular tissue attenuates ultrasound only a little more than water but that the effect of fat tissue in this respect is much higher Our results seem to be contradictory to what has been written on the absorption of muscular and fat tissue Our results apply however to ultrasonic attenuation which includes besides absorption also reflection refraction and scattering Moreover we have used at our examinations a higher frequency than was done in the most measurements of absorption mentioned above The difference may also be affected by the use of a different kind of or differently prepared fat tissue

It seems to us that muscular tissue will not cause great difficulties in the analysis of orbital echograms but one has bear in mind the high attenuation effect of fat tissue In the ultrasonic diagnosis of the orbit it is important to know the exact location position and amount of fat tissue Unfortunately our knowledge of orbital anatomy is still inadequate in this respect

Summary

In this experimental study with pig eyes we have investigated the ultrasonic attenuation caused by orbital and subcutaneous fat tissue orbital muscle tissue and water The frequencies used at examinations were 6 Mc and 8 Mc As the problem was investigated in various ways we found out that the attenuation in muscular tissue is a little higher than in water while fat tissue attenuates

ultrasound much more strongly than either of those two In the ultrasonic diagnosis of the orbit it would therefore be important to know the exact location and amount of fat tissue

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

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CAN PIGMENTARY DEPOSITS ON THE TRABECULAR MESHWORK INCREASE THE RESISTANCE OF THE AQUOUS OUTFLOW?

BY

HANS PETER PETERSEN

It is by now well known that in some types of glaucoma one can by gonioscopy find pigmentary deposits in the trabecular spaces The question naturally arises whether these pigmentary deposits have any pathogenetic significanse Opinion as to the role of pigment in the pathogenesis of glaucoma has long been *divided* The question has been brought up time and again since its first introduction by *Levinsohn* (1909) Many authors have discussed this problem among others *Koeppe* (1917 1920) *Gradle* (1921) *Barkan Boyle and Maisler* (1936) *Busacca* (194) *Sampaolesi* (1959) *Simon Tor* (1961) and *Tarkkanen* (1962) Sugar s description of a special form of glaucoma (Pigmentary glaucoma 1940 1949) with its pronounced and characteristic picture has created renewed interest for the possible pathogenetic role of the pigmentary deposits In some cases a dilatation of the pupil causes liberation of pigment granules in the anterior chamber A consecutive *acute rise in the intraocular tension* may be registered *(P Kristensen* (1961) and others) This phenomenon also gives support to the theory of pigment deposits on the trabecular meshwork as possible cause of the elevated intraocular tension

In a previous paper (Pigmentary glaucoma 1961) the author discussed the question of the possible role of the pigmentary deposits for the glaucoma The result of this analysis was that it *is impossible* to draw reliable conclusions

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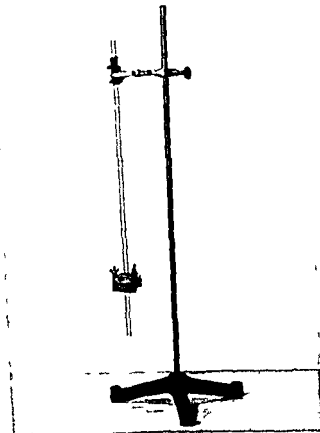


Fig 1

ment granules and when uncovered was done in the following way the glass tube was filled with physiological saline solution until about 35 cm above the filter and the time the water took to sink from the 30 cm mark to the 20 cm mark above the filter was measured A certain quantity of the pigment suspension was then mixed with physiological saline solution filled in the glass tube and the apparatus was left untouched overnight in order to let all the pigment sink down to the filter After having controlled that all the water had run through the filter the glass tube was again filled with physiological saline solution up to approximately 35 cm above the filter Then the time the water took to sink from the 30 cm mark to the 20 cm mark was measured Before each experiment the filters were changed and after the experiments each filter was checked for possible defects It was ascertained that no pigment had passed through the filter

from purely clinical observations Gonioscopy reveals only the most superficial tissue and it is not possible to determine how much pigment is deposited deeper in the outflow channels Nor is it known how much significance such a deeper deposition would have for the outflow The most important factor is that we have insufficient knowledge of the physical properties of the pigment granules Are they like coarse sand which readily allows water to seep through? Or are they of varying size so that some can readily pass through the mesh work? Or does the pigment deposition form a compact and almost impenetrable mass? It is not until these questions have been answered that it will be possible to determine whether there is obstruction of the passage to Schlemm's canal

The present work will try to solve some of the problems mentioned above through experimental research The plan for the experiment was to procure pigment granules from the iris and the ciliary corpus and then to find out whether a layer of these impedes or hinders saline water in running through a filter with approximately the same pore size as the trabecular meshwork The pigment was taken from enucleated eyes After the eye had been cut open alongside the equator and the lens and corpus vitreum carefully removed the iris and the ciliary corpus could easily be loosened from the sclera They were then put in a shallow glass bowl with the pigment layer pointing upwards After a few days the iris stuck firmly to the glass Physiological saline solution was poured over it and after an hour the pigment layer could easily be removed in big flakes by means of a glass rod The pigment was grinded fine with a "Potter L W A" The pigment granules were examined and their size determined In this way pigment granules varying in size from 1 $^1/_2\mu$ were at last procured

The filters used for the experiments are manufactured by the Millipore Filter Corporation" Bedford Massachussetts The filter which was finally chosen was "Microweb (nylon reinforced) with pore size $0\,45\,\mu \pm 0\,02\,\mu$ According to the manufacturer's description this filter has absolute surface retention of all particles larger than its pore size Microscopic and submicroscopic particles are actually screened from fluids passing through the filter The filter was put in the apparatus shown in fig 1 + 2 It contains a 35 cm long glass tube with an internal diameter of 4 8 mm The glass is cast into metal rings and kept together with metal screws Rubber packings with the same internal diameter as the glass tubes were put in between and the Millipore filter was put between these again It was by means of coloured water established before the real experiment started that the system had no leaking 2 marks 30 cm and 20 cm above the filter were put on the glass tube which inwardly was moistened with silicone The pigment granules were suspended in physiological saline solution and a standard suspension containing 16 4 pigment granules pr $^1/_{4000}$ mm^3 was used for all the tests

The examination of the difference in the flow rate when covered with pig

Therefore perfusion experiments were carried out on two eyes *in vivo* (with intraocular tumor) and on an enucleated eye For these experiments pigment granules suspended in Barany s fluid were used a barbital buffered solution of saline with pH 6 95 The electromanometric recording system is the same that has been described by *J Hetland Eriksen* (1965) A 5 ml pigment suspension containing 35 pigment granules pr $^1/_{1000}$ mm³ was made for the experiments

The first patient was a 14 month old boy with intraocular tumor General anaesthesia was given and a neddle with 0 45 mm internal diameter was inserted into the anterior chamber The needle was connected to the pressure transducer by a 6 cm long polyethylene tube The intraocular pressure of the eye could be regulated by means of a fluid reservoir filled with a barbital buffered solution of saline The pressure was raised to 40 mm Hg After 5 minutes the pressure had decreased to 30 mm Hg as can be seen in the first tonogram fig 3 The anterior chamber was then drained of fluid and 220 mm³ of the pigment suspension injected by means of an Agla micrometer syringe with the needle remaining in the anterior chamber (The pigment suspension in the anterior chamber had a dark brown colour so that the iris was almost invisible)

The pressure was raised again to 40 mm Hg As can be seen from tonogram no 2 fig 3 the pressure falls to 35 mm Hg within 1 minute and remains unchanged at the same level for 12 minutes *but after that it begins to rise slowly but clearly*

The next experiment was carried out in local anaesthesia The patient was a 41 year old woman with intraocular tumor After the needle was inserted into the anterior chamber the pressure was raised to 50 mm Hg Within 6 minutes the pressure fell to 25 mm Then the anterior chamber was drained and the pigment suspension injected in the same way as in the previous experiment The pressure was raised to 50 mm Hg As it appears from the tonogram fig 4 the pressure shows some oscillations but does not fall below 30 mm Hg But after 15 minutes the pressure begins to rise *and after 23 minutes it has reached 50 mm Hg*

An experiment was also carried out on an enucleated eye The needle was inserted into the anterior chamber and the pressure raised to 50 mm Hg Within

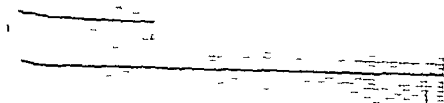


Fig 5

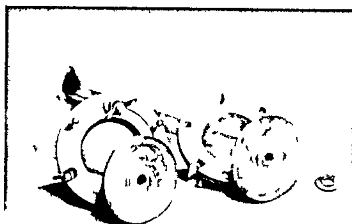


Fig 2

The results of the experiments are listed in the following table

	Flow rate of physiological saline solution without pigment suspension	Added quantity of pigment suspension	Flow rate of physiological saline solution after adding pigment
1	5 min 45 sec	1 ml	55 min
2	6 min 40 sec	1 ml	59 min
3	5 min 25 sec	0 5 ml	16 min 55 sec
4	5 min 32 sec	0 5 ml	20 min 30 sec
5	6 min 30 sec	0 5 ml	22 min 30 sec
6	5 min 55 sec	0 25 ml	17 min 28 sec
7	5 min 32 sec	0 25 ml	16 min 20 sec
8	6 min 30 sec	0 10 ml	16 min 16 sec
9	5 min 16 sec	0 10 ml	15 min 10 sec
10	6 min 12 sec	0 10 ml	16 min 10 sec
11	5 min 15 sec	0 10 ml	14 min 30 sec
12	5 min 30 sec	0 10 ml	14 min 35 sec

It appears that pigment granules on the filter reduce the flow rate and the water seeps slowlier through the filter as greater quantities of pigment are added Even a modest amount will reduce the flow rate But as the filter is stiff and inelastic it is uncertain whether the result of these experiments applies to the eye *in vivo* as well especially since the trabecular meshwork is not like a rigid grid

hinder the flow of saline water through this filter *In vivo* the intraocular tension rises after pigment suspension has been injected into the anterior chamber Pigment suspension injected into the anterior chamber of an enucleated eye will retard the outflow of water

The results of the experiments seem to indicate that pigment granules on the trabecular meshwork *in adequate amounts* represents an obstruction to the aqueous outflow

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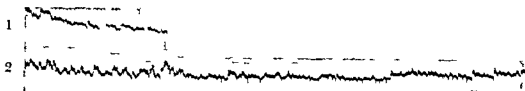


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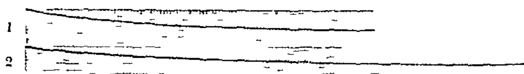


Fig 5

16 minutes the pressure fell to 20 mm Hg The anterior chamber was drained and the pigment suspension was injected The tonogram in fig 5 shows that 30 minutes elapse before the pressure falls to 20 mm that is to say twice the time it took without pigment

All the eyes were submitted to histologic examination after the experiments and pigment granules were found many places partly on partly within the trabecular meshwork Other places the pigmentary deposits were more sparse

In conclusion from what has been described above there is reason to believe that pigmentary deposits in *sufficient quantities* are capable of increasing the resistance of the aqueous outflow thus being of pathogenetic significance for some types of glaucoma But one cannot rule out the possibility that the pigment quantities used in these experiments exceed the quantities found in this type of glaucoma

What quantity of pigment granules on the trabecular meshwork is needed remains to be determined This quantity is likely to vary as a rigid trabecular meshwork stands a lesser quantity of pigmentary deposits than a lithe and yielding one

Summary

The problem concerning the possible cause of elevated intraocular tension by pigmentary deposits on the trabecular meshwork is discussed Experiments in *vivo* and *in vitro* have been performed Pigment granules lying on a filter

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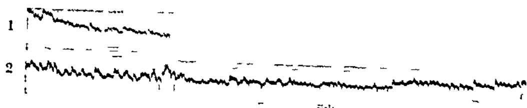


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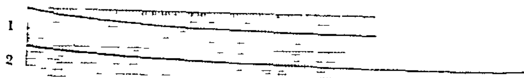


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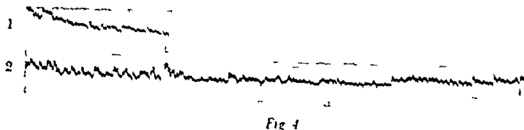


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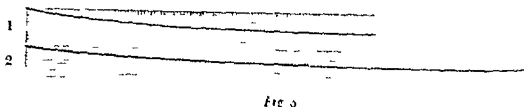


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Material and methods

With the object of clarifying any possible influence exerted by the efferent fibres on the control of ocular tension we studied a series of patients who had sustained total unilateral optic nerve lesions resulting in lack of sensibility to light and suspended direct but maintained consensual pupillary reaction in the eye with the nerve lesion In most cases the loss of visual function had occurred suddenly in connection with a slight skull injury supposedly complicated by a fracture through the optic canal although most frequently such a fracture cannot be revealed roentgenologically We had opportunity of seeing only very few of the patients shortly after the injury the remaining patients were not summoned till months or years had elapsed after the accident In order to examine whether the blood supply was equal in both eyes all patients underwent ophthalmodynamometry and in few cases oculosphygmography and electroretinography were carried out but no difference between the two eyes was demonstrated In no case was the difference in tension between the two eyes higher than 2 mm

If in such eyes which are normal in all other respects a difference in ocular tension is observed it must be considered most likely to be a result of a disruption of the influence on the eye through the efferent nerve fibres on the damaged side

Results

Our *first patient* was a 54 year old man who following a slight skull injury had lost visual function in one eye a few days before the examination Determination of the tension revealed *identical values 10* mm in both eyes Subsequent water drinking test showed an *increase in tension of 8 mm* in the intact eye while the increase was doubtful in the eye with the optic nerve lesion Repeated water drinking tests carried out after one week and again one month later gave similar results although the increase was somewhat lower in the sighted eye (Fig 1) *The 24 hour* curve gonioscopy and tonography all showed normal conditions and since during water drinking tests the tension never reached values above 20 mm appl the possibility of glaucoma could be excluded Ophthalmodynamometry and electroretinography showed normal values and were identical in both *eyes*

Subsequently we have carried out water drinking tests in an additional 12 patients of this type The tension curves for both eyes of all the patients are shown in Fig 2 and Fig 3 presents average curves for the eyes with the optic nerve lesions and for the healthy eyes Eyes with optic nerve lesions presented

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the Eye Department Rigshospitalet University of Copenhagen (Head Professor H Ehlers M D) and the Eye Department Kommunehospitalet Copenhagen (Head Professor P Brændstrup M D)

INTRAOCULAR PRESSURE IN UNILATERAL OPTIC NERVE LESION

BY

DAG RIISE and SVEND ERIK SIMONSEN

Several studies have shown concordantly that by stimulation of the hypo thalamus changes in the intraocular pressure can be produced in experimental animals (*Schmerl* & *Steinberg* (1950) *Nagai Ban* & *Kurotsu* (1951) von *Sallmann* & *Lowenstein* (1955) *Gloster* & *Greaves* (1957)) Further details of the underlying mechanism are not known The existence of efferent nerve fibres from the brain via the optic nerve to the retina has been demonstrated in insects cephalopodes and birds (*Cajal* (1911) *Bullock* & *Horridge* (1965) *Trujillo Cenoz* (1965), *Dowling* & *Cowan* (1966) *Simonsen* (1967) *Ogden* (1968))

As to whether similar efferent fibres exist in the human optic nerve is still open to discussion In a number of histological studies *Wolter* (1965) believed it possible to demonstrate the presence of efferent fibres in the human optic tract the chiasma the optic nerve and the retina This assumption was supported firmly by *Ventura* & *Mathieu* (1959) and *Honrubia* & *Elliott* (1965) who used the flat mount technique Both *Granit* (1962) and *Cogan* (1967) were of the opinion that efferent fibres to the retina existed in man whereas *Dowling* & *Boycott* (1966) were more sceptical

If such efferent fibres do exist in man they must be regarded as tracks of impulses from the brain via the optic nerve to the retina where they seem to end mainly in the intermediary layers of the retina (*Wolter* (1965) and *Honrubia* & *Elliot* (1968))

Material and methods

With the object of clarifying any possible influence exerted by the efferent fibres on the control of ocular tension we studied a series of patients who had sustained total unilateral optic nerve lesions resulting in lack of sensibility to light and suspended direct but maintained consensual pupillary reaction in the eye with the nerve lesion In most cases the loss of visual function had occurred suddenly in connection with a slight skull injury supposedly complicated by a fracture through the optic canal although most frequently such a fracture cannot be revealed roentgenologically We had opportunity of seeing only very few of the patients shortly after the injury the remaining patients were not summoned till months or years had elapsed after the accident In order to examine whether the blood supply was equal in both eyes all patients underwent ophthalmodynamometry and in few cases oculosphygmography and electroretinography were carried out but no difference between the two eyes was demonstrated In no case was the difference in tension between the two eyes higher than 2 mm

If in such eyes which are normal in all other respects a difference in ocular tension is observed it must be considered most likely to be a result of a disruption of the influence on the eye through the efferent nerve fibres on the damaged side

Results

Our first patient was a 54 year old man who following a slight skull injury had lost visual function in one eye a few days before the examination Determination of the tension revealed identical values 10 mm in both eyes Subsequent water drinking test showed an *increase* in tension of 8 mm in the intact eye while the increase was doubtful in the eye with the optic nerve lesion Repeated water drinking tests *carried out* after one week and again one month later gave similar results although the increase was somewhat lower in the sighted eye (*Fig 1*) The 24 hour curve gonioscopy and tonographs all showed normal conditions and since during water drinking tests the tension never reached values above *20 mm appl* the possibility of glaucoma could be excluded Ophthalmodynametry and electroretinography showed normal values and were identical in both eyes

Subsequently we have carried out water drinking tests in an additional 12 patients of this type The tension curves for both eyes of all the patients are shown in Fig and Fig 3 presents average curves for the eyes with the optic nerve lesions and for the healthy eyes Eyes with optic nerve lesions presented

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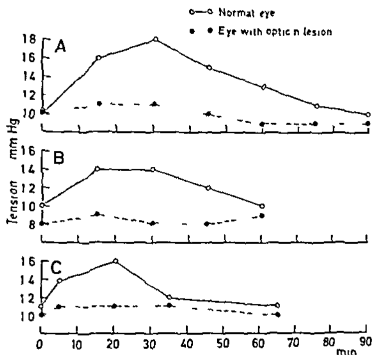


Fig 1
Water drinking test taken 1 week (A) 2 weeks (B) and 1 month (C) after optic nerve lesion

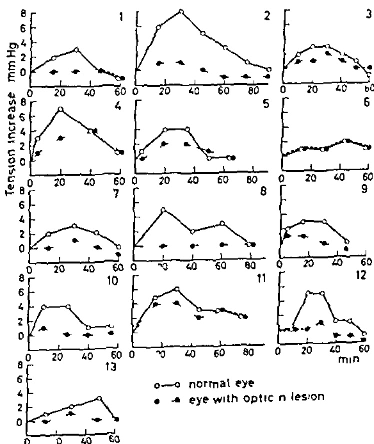


Fig 2
Water drinking test in 13 patients with unilateral optic nerve lesion

one A hypothesis is advanced according to which the water drinking tests exerts its influence via a centre in the hypothalamus which is sensitive to the osmotic pressure and from there via efferent fibres in the optic nerve

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Grimes (1958). Through experiments involving cutting and stimulation of nerves, pressure regulating nerve fibres were found in the sympathetic nervous system and in the trigeminal nerve *(von Sallmann Marci Wanco & Grimes* (1956) *Perkins* (1957) and *Gloster & Greaves* (1958)). However, the presence of these fibres does not explain our findings.

Presumably, the influence of the water drinking test on the intraocular pressure is a function of the osmotic pressure of the blood but it is not yet known whether the influence is exerted directly on the ciliary body or indirectly via a cerebral centre which is sensitive to the osmotic pressure. On the basis of clinical observations *Thiel & Hollwich* (1955) supposed that the drinking water test exerts its influence via the hypothalamus. From renal physiology it is known that a centre sensitive to the osmotic pressure of the blood exists in the nucleus supraopticus which controls the renal excretion of water (*Woods Bard & Bleier* (1966)). The supra optic nucleus actually lies close to the posterior surface of the optic chiasma and consequently in the early literature it was called the "basal optic ganglion" (*Meynert* (1872)). It is not known whether this nucleus also exerts an influence on the control of ocular tension.

The fact that in our experiments an isolated lesion of the optic nerve prevents water drinking tests from exerting influence on the eye with the nerve lesion gives rise to the impression that the efferent fibres of the optic nerve might influence the tension. Anatomically, some of these fibres have been traced from the hypothalamus to the retina: *Wolter* (1965) *Ventura & Malieu* (1959) and *Honrubia & Elliott* (1968) have traced the fibres as far as to branches in the ora serrata. Since the ciliary body is covered by two layers of neuroretinal epithelium a possible influence of the inflow of the acqueous humour via these intraretinal fibres cannot be excluded. Our hypothesis that the water drinking test exerts its influence via a centre in the hypothalamus which is sensitive to the osmotic pressure and from there via efferent fibres in the optic nerve cannot be considered to be proved although the results of our study might suggest that this is the case. The anatomical conditions and other experiments do not decisively contradict this assumption.

We are now testing the theory by means of animal experiments in which we produce an ocular increase in tension by stimulation of the hypothalamus in rabbits followed by repeated experiments after unilateral cutting of the optic nerve.

Summary

Water drinking tests in patients with unilateral total optic nerve lesion produce a less pronounced increase in tension on the damaged side than on the healthy

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From Carlanderska Sjukhemmet Gothenburg Sweden

SILICONE INJECTION INTO THE VITREOUS IN HOPELESS CASES OF RETINAL DETACHMENT

BY

BENGT ROSENGREN

With conventional operative methods healing is not achieved in all cases of detachment of the retina Treatment is ineffective in 10 20 % and it is for these cases that one would wish to have available a method that would result in at least some degree of visual acuity The attempts that have been made to inject silicone fluid into the vitreous have aroused some hopes

The idea underlying these attempts has been to make the detached layer of the retina regain contact with the pigmented epithelium by means of this transparent fluid Dow Corning 360 (specific gravity 0 972) To accomplish this the fluid must however possess such properties that it does not pass through the retinal rupture. The forces which counteract such passage are the surface tension and to some degree the viscosity

The surface tension depends on the fact that molecules in the surface layer are attracted towards the interior of the liquid the surface layer then acting as an elastic membrane The stronger is the curvature of the liquid surface the more strongly does the surface tension assert itself the smaller is a rupture the more definitely does this force act as an impediment to passage

Unfortunately the surface tension coefficient of the silicone fluid in relation to water is only about 47 (whereas the corresponding figure for air/water is 75) The surface tension coefficient of silicone fluid vitreous may be still lesser because of the protein content of the vitreous and since this factor varies

Trujillo Ceno O Some aspects of the structural organization of the intermediate retina of dipterans J Ultrastruc Res *13* 1 (1965)
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At present there is no possibility of judging how strong is the motivation underlying the fairly dramatic method consisting of introducing an injection needle close to the optic disc It has been stressed in support of this method that it is an essential problem to pass behind the membranes in the vitreous As far as we learn to avoid such membranes this type of injection may be less actual

Results

In the following account particular attention will be focused on the two largest series now existing One is that of Dr E Okun St Louis U S A and the other is that of Professor O E Lund Essen West Germany

The St Louis series comprises 304 cases in 74 of which (24 %) there was an improvement in visual acuity to at least finger counting In 67 of them the visual acuity during a period of 6 mounts to 5 years was finger counting or walking vision no mention was made of the number of cases in which there was an improvement to reading vision A remarkable feature is that anatomical reattachment of the retina occurred in 51 cases (17 %) without any improvement in visual acuity

As far as complications are concerned I shall not dwell on those associated with the intervention but will confine myself to so called late complications Cataract appeared in 51 % usually in the form of nuclear sclerosis or post sub capsular opacities The changes in the lens developed relatively slowly and in some cases several years elapsed before they were noticeable Corneal dystrophy occurred chiefly in aphakic eyes and secondary glaucoma was observed in 31 eyes 29 of them were aphakic

Finally it can be mentioned that 9 eyes were enucleated and examined histologically Only an inappreciable reaction to the *silicone fluid* was present

Okun summarized his report with the statement that only one eyed individuals should be submitted to this *treatment* In cases *in* which the visual acuity of the fellow eye was good possible complications in the silicone treated eye might be troublesome to the patient

Professor Lund s series from Essen comprises 93 eyes The amount of silicone *fluid injected was* 2 4 ml i e greater that that in the American series The visual acuity improved in 24 % *in 3 cases* to reading vision Among the complications mention was made of corneal dystrophy chiefly in aphakic eyes as well as a few cases of secondary glaucoma these were relatively amenable to treatment

To these I can add my own *series* consisting merely of 12 cases The visual acuity failed to improve in *i* of them In one *it improved to* finger counting at

no generally applicable value can be given It is however known – on the basis of observations of silicone drops in the anterior chamber which are delimited in relation to the fluid and tissue – that the surface tension is a factor to be taken into account Nevertheless the surface tension can be presumed to be relatively low, a circumstance which indicates that silicone injections are suitable chiefly in cases with small ruptures

The viscosity is another factor of importance It depends on the internal friction in the fluid and if the viscosity is high *i e* if the fluid is viscous this can greatly prolong passage through the rupture and with rapidly transient changes in pressure passage can be prevented With permanent pressure *e g* in the presence of shrinkage processes in the retina the effect is on the other hand uncertain The silicone fluid used has a viscosity of 1000 2000 cs but a viscosity of up to 10 000 cs is also employed

Technique

As a rule a method similar to Shafer s procedure for injection of the vitreous is used A meridional incision is made through the posterior part of the pars plana and a 20 gauge injection needle is introduced through it about 6 mm from the limbus For the silicone injection a needle with a blunt tip is used under ophthalmoscopic control it is advanced through the central parts of the eyeball to its posterior parts to pass behind any existing membrane formations in the vitreous body The quantity of silicone fluid injected is given by Okun as 1-1 5 ml Drainage of the subretinal fluid is often done as well

Personally I prefer another method *i e* fractionated injection of silicone fluid In view of the high viscosity of the fluid a syringe with small piston diameter (5 mm) is used this permits stronger pressure on injection A fine relatively short needle (25 gauge) is introduced through the posterior part of the ciliary body – as in air injection – and the quantity of fluid injected is generally 0 20 0 30 ml As a rule the rise in intraocular pressure which occurs on injection does not allow a larger quantity It is checked that after injection the pressure falls within a few minutes to below the arterial pressure With this method one can by means of repeated injections into the vitreous introduce several ml Although theoretically one should be able to fill the whole vitreous a limit is set by the existing risk of a rise in intraocular pressure The repeated injections are made at approximately the same place usually at 12 o clock 5 mm from the limbus so that one avoids separate silicone bubbles in the vitreous When the injection is performed every other day the duration of treatment is 3 4 weeks

At *present* there is no possibility of judging how strong is the motivation underlying the fairly dramatic method consisting of introducing an injection needle close to the optic disc It has been stressed in support of this method that it is an essential problem to pass behind the membranes in the vitreous As far as we learn to avoid such membranes this type of injection may be less actual

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1 metre and in another to finger counting at 1 2 metres although with only central remains of the visual fields In an additional case, walking vision was achieved but it was lost after a short time due to a new large rupture with recurrence In two patients, however, there was an improvement to reading vision I treated one of them in cooperation with Dr Seedorff of Copenhagen I have been able to follow up the other case of reading vision for 3 years The visual acuity is now 0 1 and the patient who is aphakic and high myopic can read Jaeger 4

A survey of the aforementioned series indicates that with silicone injection one can count on an improvement in visual acuity in about 1/4 of the cases It is also evident that the complications are less frequent and less serious one could presume initially

A strange feature is the group of cases with anatomical reattachment of the retina but without improved vision which is difficult to explain It cannot be determined at present whether a toxic factor comes into effect through the silicone fluid Another possibility is however, that true reattachment of the retina has not occurred but that a slight amount of subretinal fluid still persists It should be of interest to examine such cases carefully with a contact lens to ascertain whether the retina has in fact completely regained contact with the pigmented epithelium

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INTRACAPSULAR CATARACT EXTRACTION BY THE CRYOTECHNIQUE AND OTHER METHODS

A Comparative Study of 826 Cases

BY

H H SEEDORFF and B LAWÆTZ

By now cataract extraction by the cryotechnique seems to have been accepted in most eye departments From the time that this method was first introduced by *Krwawicz* (1961 and 1963) many authors have dealt with the problems which had to be overcome until cryotechnique was finally established Among these authors there are *Kelman & Cooper* (1963) *Bellows* (1964) *Machemicius* (1963) Radnot et al (1966) and from Scandinavia *Rosengren* (1964) *Rosengren & Enoksson* (1966) *Viggo Jensen* (1965) and *Seedorff* (1965)

While the principle of cryosurgery was soon generally accepted with some hesitation in certain quarters it is true (e g M Lean 1964) some years elapsed until the experience was so advanced that a suited and reliable apparatus was constructed This refers primarily to the fact that the advanced instruments in use now have minimized the risk of damaging the cornea and iris which originally was the main objection to the cryotechnique

In perusing the literature on cryotechnique one cannot help noting that only a relatively few studies have been concerned with comparing the therapeutic results obtained by cryosurgery and by conventional methods (capsule forceps or erisiphake) An exception is *Worthen & Brubaker's* (1968) study These authors performed a retrospective analysis of 2000 cataract extractions

half done by cryomethods and the remainder by other conventional methods. They arrived at the result that capsular rupture was less common in the cryo operated material, but apart from that they found no differences between the two principles of extraction Another study by *Skrzypczak et al* (1968) reports a similar comparison but in a smaller series They found not only that capsular rupture was less apt to occur in cryoextraction but also demonstrated a reduction in the loss of vitreous from 8 7 % to 2 % It is pointed out furthermore that zonulolysis by chymotrypsin seems less necessary in the cryotechnique than with the use of capsule forceps

The present study was carried out as a comparative retrospective investigation according to similar principles as used in the two last mentioned ones In our study, we went a step further not being content with the course of the operation but we have extended the study to comprise also the postoperative phase and the final visual results In our opinion it is only by such comprehensive criteria that the advantages and drawbacks of the cryotechnique can be properly evaluated

It was inevitable that in view of our experience we were somewhat biassed Therefore in order to set up the study in a way as objective as possible we coded all data from the case records on punch cards Thereafter the results were analysed in their entirety In other words the results of assessing the 413 operated eyes which represent the cryoectractions were not known until the results were available for the control series i e the remaining 413 (operated upon by forceps or erisiphake)

Present Investigations

As already mentioned the material comprises a total of 826 eyes subjected to cataract surgery This is almost the total number of cataract operations performed during the period from February 1963 to May 1968 413 of these 826 *cataracts were extracted by a cryotechnique* and represent the total number of operations done by this technique in the Department As stated in the introduction we wished to compare the incidence of complications operative as well as postoperative of the cryotechnique with that of complications occurring in an equally large operated series (413) treated by conventional surgical techniques i e capsule forceps and erisiphake (control series)

Fig 1 shows in a column diagram how many of the 826 operations were done by cryotechnique or by forceps or erisiphake The figure shows the development through the years int al that from the middle of 1967 cryosurgery was introduced as the standard method

We do not propose to deal with details of the operative procedure or to discuss technical niceties in this connection For the sake of continuity however it must be mentioned that all 826 operations were carried out under the same

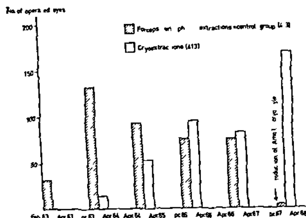


Fig 1

Chronological grouping og 8?6 cataract extractions performed during the period February 1963 to April 1963

local anaesthesia (retrobulbar + akinesia) using the same suturing technique (McLean suture) opening of the chamber (keratome and scissors) and iridec tomy (iridotomy) etc The only therapeutic difference is that in half the ope rations the lens was extracted by a cryoinstrument and in the other half (the control series) by forceps or erisiphake Moreover it may be mentioned that from 1963 until April 1967 we used the apparatus designed by *Krwawicz* (1961) for the cryoextractions while from April 1967 all cryoextractions have been performed by Amoils cryostylet

The two materials of 413 cases each are listed in more detail in Table 1 which shows that in respect to age and morphology of the cataract the two groups are almost identical If the complicated cases are separated from each group there were 129 such cases in the cryooperated and only 86 in the control group Further comments on these two values will follow below Diabetic cataracts are listed in a separate group

We decided to divide the 2 × 413 operated eyes according to the morphology of the cataract and thereafter schematically recording the operative course (Table ?) the postoperative phase (Table 3) and lastly the final visual result (Table 4)

Table 2 shows on the left the auxiliary measures used in the operation while on the right it lists the complications which occurred in connection with the operation itself

In Table 3 the materials still by morphology of cataract are analysed by postoperative complications transient or more permanent. Thus the table also

half done by cryomethods and the remainder by other conventional methods. They arrived at the result that capsular rupture was less common in the cryo operated material but apart from that they found no differences between the two principles of extraction Another study by *Skrzypczak et al* (1968) reports a similar comparison but in a smaller series They found not only that capsular rupture was less apt to occur in cryoextraction but also demonstrated a reduction in the loss of vitreous from 8 7 % to 2 % It is pointed out furthermore that zonulolysis by chymotrypsin seems less necessary in the cryotechnique than with the use of capsule forceps

The present study was carried out as a comparative retrospective investigation according to similar principles as used in the two last mentioned ones In our study we went a step further not being content with the course of the operation but we have extended the study to comprise also the postoperative phase and the final visual results In our opinion it is only by such comprehensive criteria that the advantages and drawbacks of the cryotechnique can be properly evaluated

It was inevitable that in view of our experience we were somewhat biassed Therefore in order to set up the study in a way as objective as possible we coded all data from the case records on punch cards Thereafter the results were analysed in their entirety In other words the results of assessing the 413 operated eyes which represent the cryoextractions were not known until the results were available for the control series i e the remaining 413 (operated upon by forceps or erisiphake)

Present Investigations

As already mentioned the material comprises a total of 826 eyes subjected to cataract surgery This is almost the total number of cataract operations performed during the period from February 1963 to May 1968 413 of these 826 cataracts were extracted by a cryotechnique and represent the total number of operations done by this technique in the Department As stated in the introduction we wished to compare the incidence of complications operative as well as postoperative of the cryotechnique with that of complications occurring in an equally large operated series (413) treated by "conventional surgical techniques i e capsule forceps and erisiphake (control series)

Fig 1 shows in a column diagram how many of the 826 operations were done by cryotechnique or by forceps or erisiphake The figure shows the development through the years int al that from the middle of 1967 cryosurgery was introduced as the standard method

We do not propose to deal with details of the operative procedure or to discuss technical niceties in this connection For the sake of continuity however it must be mentioned that all 826 operations were carried out under the same

Table 3

Postoperative course after cataract extraction using cryotechnique or else forceps or erisiphake — control group

Type of cataract	Permanent corneal oedema		Corneal dystrophy		Flat chamber		Hyphaema		Iris prolapse		Secondary cataract		Cyclitic reaction		Secondary glaucoma		Phthisis		Total cases operated	
	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.
Immature	34	62	0	5	14	38	64	71	3	9	19	57	24	45	4	5	0	2	219	264
Mature/hypermature	28	38	1	1	14	21	35	36	3	4	15	34	23	20	3	3	2	0	194	149
Total	62	100	1	6	28	59	99	107	6	13	34	91	47	65	7	8	2	2	413	413

Table 4

Visual acuity obtained after cataract extraction by cryotechnique and by forceps or erisiphake = control series

Type of cataract	6/6 – 6/12		6/15 – 6/24		6/30 – 6/60		6/60 – 3/60		< 3/60		Total cases operated	
	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control
Immature	13	149	49 (25 retinal deg.)	62 (22 retinal deg.)	21 (16 retinal deg.)	26 (10 retinal deg.)	11 (8 retinal deg.)	18 (10 retinal deg.)	4 (3 retinal deg.)	8 (4 retinal deg.)	219	263 ¹)
Mature	1?9	7	45 (20 retinal deg.)	32 (15 retinal deg.)	17 (11 retinal deg.)	25 (8 retinal deg.)	9 (5 retinal deg.)	9 (5 retinal deg.)	4 (3 retinal deg.)	6 (3 retinal deg.)	194	149
Total	253 61 %	226 55 %	94 23 %	94 23 %	38 9 %	51 12 %	20 5 %	27 7 %	8 2 %	14 3 %	413	412 ¹)

¹) 1 died before visual acuity was determined

cular the sequelae of iridocyclitis – were more common in the cryotreated material (Table 1) and indeed synechiotomy was more often needed in this group. The distribution of complicated cases between the two groups incidentally stresses that the cryotreated material is by no means a selection of less complicated cases – on the contrary. Zonulolysis by chymotrypsin was used in 108 of the cases treated by cryosurgery as compared with 169 treated by forceps or phake extraction. In this connection it should be borne in mind that the age distribution is largely the same in both materials so that the cryotreated material does not contain fewer young cataract eyes than the control series.

Further analysis of Table 2 shows that capsular rupture occurred in only 10.1 % of the cases treated by cryosurgery while it occurred in 30.3 % of those treatment by other methods of extraction.

Table 1

Grouping of the cryooperated eyes as well as of the forceps and erisiphake operated eyes (control series)

Cryooperated eyes

Number 413 eyes

Age distribution

30 59 years 105
60 69 years 115
70 years and over 193

Grouping by morphology:

Immature cataracts 219
Mature and hypermature (intumescent) 194

Complicated cataracts

129 31 %

Diabetic cataracts

25 6 %

Forceps or erisiphake operated eyes (Control series)

Number 413 eyes

Age distribution

30 59 years 84
60 69 years 121
70 years and over 208

Grouping by morphology

Immature cataracts 264
Mature and hypermature (intumescent) 149

Complicated cataracts

86 21 %

Diabetic cataracts

21 5 %

Table 2

Course of operation in a total of 826 cataract extractions grouped by extraction principle (cryo or forceps/erisiphake viz control series)

Type of cataract	Chymotrypsin zonulolysis		Synechotomy		Capsule rupture		Contact with cornea	Loss of vitreous		Loop extraction		Total cases operated	
	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Cryo	Control	Cryo	Control	Cryo	Control
Immature	62	113	20	7	25	69	8	5	30	0	11	219	264
Mature hypermature	45	56	18	4	21	52	7	5	10	0	0	194	149
Total	108	169	38	11	46	121	15	10	40	0	11	413	413

affords information about complications which persisted after discharge requiring out patient treatment and follow up for a varying length of time

Table 4 sets out the final visual acuity and in brackets below some of the figures – the less favourable and poorest vision – how many within each group had central retinal degenerations (arteriosclerosis diabetic changes etc)

Comments on tables 1, 2 3 and 4

In the introduction it was stated that complicated cases of cataract – in parti

Table 3

Postoperative course after cataract extraction using cryotechnique or else forceps or erisiphake = control group

Type of cataract	Transient corneal oedema		Corneal dystrophy		Flat ant. Chamber		Hyphaema		Iris prolapse		Secondary cataract		Cyclitic reaction		Secondary glaucoma		Phth		Total cases operated	
	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.
Immatur	34	62	0	5	14	38	64	71	3	9	19	57	24	45	4	5	0	2	219	264
Matur hypermature	28	38	1	1	14	21	35	36	3	4	15	34	23	20	3	3	2	0	194	149
Total	62	100	1	6	28	59	99	107	6	13	34	91	47	65	7	8	2	2	413	413

Table 4

Visual acuity obtained after cataract extraction by cryotechnique and by forceps or erisiphake = control series

Type of cataract	6/6 – 6/12		6/18 – 6/24		6/30 – 6/60		6/60 – 3/60		< 3/60		Total cases operated	
	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control
Immatur	134	149	49 (25 retinal deg.)	62 (22 retinal deg.)	21 (16 retinal deg.)	26 (10 retinal deg.)	11 (8 retinal deg.)	18 (10 retinal deg.)	4 (3 retinal deg.)	8 (4 retinal deg.)	219	263 1)
Mature	119	77	45 (20 retinal deg.)	32 (15 retinal deg.)	17 (11 retinal deg.)	25 (8 retinal deg.)	9 (5 retinal deg.)	9 (5 retinal deg.)	4 (3 retinal deg.)	6 (3 retinal deg.)	194	149
Total	253 61 %	226 55 %	94 23 %	94 23 %	38 9 %	51 12%	20 5 %	27 7 %	8 2 %	14 3 %	413	412 1)

1) 1 died before visual acuity was determined

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Further analysis of Table 2 shows that capsular rupture occurred in only 10.12 % of the cases treated by cryosurgery while it occurred in 30.37 % of those treatment by other methods of extraction.

Table 1

Groupıng of the cryooperated eyes as well as of the forceps and erısıphake operated eyes (control serıes)

Cryooperated eyes

Number 413 eyes

Age distribution

30 59 years 105
60 69 years 115
70 years and over 193

Grouping by morphology

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Complicated cataracts

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Forceps or erisiphake operated eyes
(Control se s)

Number 413 ey

Age distribution

30 59 yea s 84
60 69 years 121
70 years and over 208

Grouping by morphology

Immat re cata acts 264
Mature and hyperm tu (tumesc t) 149

Complicated cataracts

86 21 /

Diabetic cataracts

21 5 /

Table 2

Course of operatıon ın a total of 826 catarıct extractıons grouped by extractıon prıncıple (cryo or forceps/erısıphake vız control serıes)

Type f cata act	Chymotryp zo loly i		Sy h i my		Cap l ruptu		Contact w th ir s / ne	L ss f vitreous		Loop tra tio		T t l cases ope ated	
	Cryo	Co trol	Cry	Control	Cryo	Control	Cryo	Cryo	Control	Cryo	Control	C yo	Control
Immat re	62	113	20	7	25	69	8	5	30	0	11	219	264
Matu hyp matur	46	56	18	4	21	52	7	5	10	0	0	194	149
T tal	108	169	38	11	46	121	15	10	40	0	11	413	413

affords ınformatıon about complıcatıons whıch persısted after dıscharge re quırıng out patıent treatment and follow up for a varyıng length of tıme

Table 4 sets out the fınal vısual acuıty and ın brackets below some of the fıgures – the less favourable and poorest vısıon – how many wıthın each group had central retınal degeneratıons (arterıosclerosıs dıabetıc changes etc)

Comments on tables 1 2 3 and 4

In the ıntroductıon ıt was stated that complıcated cases of cataract – ın partı

(1) immature and (2) mature or hypermature (intumescent) cataract In respect to the most advanced cases of cataract one might *a priori* expect in a certain number of cases difficult operative conditions (capsule rupture synechiae etc) and consequently perhaps also an icreased incidence of postoperative complications

This analysis showed significant differences in the course of treatment in only 2 respects and only within one of the groups (control group) It is evident that capsule rupture was more common in the more mature cataracts 35 % and 27 % respectively and that loop extraction was used in 11 cases of the immature cataracts and in no case of the more mature ones In the cryomaterial on the other hand such a difference in the course of the operation was not demonstrable

Thereafter we tried to elucidate the suitability of cryotechnique in the operation of selected (complicated) cases of cataract A above the therapeutic result will be compared with that in a similar selected material from the control group

It has already been stated that the cryooperated material included 129 complicated cases as compared with only 86 in the control series The subsequent tables (5 6 and 7) are built up like Tables 2 3 and 4 – only the maturity of the cataract is replaced by the type of complications Table 5 first half shows that synechiotomy was used in approximately the same percentage of both

Table 5

Course of operation in complicated cases of cataract treated by cryotechnique or by forceps erisiphake = control group

Type of Complication	Chymotryp[illegible]		Synechotomy		C[illegible] rupture		Contact with iris/cornea	Lo[illegible] of [illegible]		Loop [illegible]		Total cases oper[illegible]	
	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Cryo	Control	Cryo	Control	Cryo	Control
Seg[illegible]	8	1	24	8	4	5	1	0	4	0	0	39	14
Pr[illegible] gl[illegible]	5	2	3	3	3	8	3	2	2	0	0	21	14
Di[illegible] of [illegible]	0	0	0	0	2	1	0	0	1	0	0	11	1
[illegible]	1		4		1		0	0		0		4	0
[illegible] detachment	0	1	0	0	0	0	0	0	0	0	0	3	1
[illegible]	11	31	1	0	4	16	1	0	9	0	3	51	56
[illegible]	25	35	32	11	14	30	5	2	16	0	3	129	86
[illegible] ca[illegible]	7	12	1	0	6	11	1	0	0	0	0	25	21

Contact with the iris or cornea relates in the main to the cryomethod This occurred in 15 cases but with serious permanent sequelae in only one The other 14 patients had no permanent changes of the tissue which had been accidentally touched by the instrument This probably the most serious complication of cryosurgery has been further diminished after a more advanced technical equipment has been introduced Vitreous loss, great or slight occurred in 40 cases of the control series and in only 10 of the cryoextraction series Loop extraction is closely related to loss of vitreous The study showed that while 11 such extractions were performed in the control series not one had to be done in the cryoextractions not even in the presence of existing dislocation or subluxation of the lens

In Table 3 it is worth noting that postoperative corneal oedema was more common in the control series (100 as compared with 62 in cryoextraction)

A flat anterior chamber was twice as common in the control series as in the cases treated by cryosurgery perhaps because cryotechnique permits a more gentle treatment of the tissues than do the conventional methods

The presence of hyphaema for a varying period after the operation was of approximately the same frequency in both groups

Iris prolapse on the other hand occurred in only 6 cases treated by cryoextraction but in 13 of the control cases It is rather difficult to find the explanation but it is presumably again the gentler treatment of the tissues by the cryomethod

The larger number of secondary cataracts in the non cryotreated material is a direct consequence of the larger number of capsule ruptures in this group

A brief or somewhat longer lasting postoperative cyclitic reaction was rather more common in the control group The incidence of secondary glaucoma was the same in both groups and so was the number of eyes which progressed to phthisis

Table 4 lists the final visual acuity In this connection most interest attaches to the percental distribution within each acuity group (6/6 6/12 etc) since as already mentioned regard was paid to possible retinal degenerations in both groups According to this table the visual results were equally good with cryotechnique and with capsule forceps (erisiphake) However it must be borne in mind that the cryomaterial included a larger number of retinal degenerations and also as apparent from Table 1 a considerably larger number of complicated cases

So far the analysis of Tables 2 3 and 4 has aimed exclusively at a comparison of the operative result in the 2 × 413 operated eyes

As is apparent from the tables the two groups (cryo and control group) were subdivided by cataract morphology This was done in order to investigate whether the maturity of the cataract within each group influenced the operative course and the results obtained In this division a distinction was made between

series Something different applies to chymotrypsin zonulolysis This procedure was found to be indicated in a higher percentage of cases in the control than in the cryoseries

Complications during the operation are presented in Table 5 Capsule rupture occurred 3 times and loss of vitreous 9 times more often in the control group than in the cryooperated group Loop extraction was used in 3 cases of the control group and in no case of the other

In 5 cases of the cryooperated material contact with the iris or cornea occurred and one of these eyes subsequently progressed to phthisis while the other 4 do not exhibit lasting damage

In respect to the course of the operation cryotechnique proved to be far superior to the forceps and phake techniques even in spite of the one serious complication reported above The postoperative course is given schematically in Table 6 It is worth noting as also emphasized above (Table 3) that postoperative corneal oedema occurred more often in the control than in the cryooperated series The more common occurrence of iris prolapse in the eyes operated upon by forceps or erisiphake is perhaps due to chance but it should be noted

No further comments will be made on the difference in the occurrence of secondary cataract in the two series as it is merely a simple consequence of the more common capsule rupture in one series On the other hand cyclitic reaction was twice as common in the control series as in the cryoseries Indeed it is our definite impression that now after the introduction of cryoextraction postoperative reaction is less marked than previously already the first time the dressing is changed

Where the postoperative course is concerned it must be concluded that in complicated cases of cataract too the incidence of transient as well as more prolonged complications was lower after cryoextraction

Table 7 lists the final visual acuity As in Table 4 a correction for the presence of central changes was attempted Thus analysed the two materials do not appear to show demonstrable changes but it must be borne in mind that the nature of the complications was heavier in the cryoseries

Let it be mentioned at last that the group of complicated cataracts includes a special category viz cataracts of diabetic origin (Tables 5 6 and 7) The number of cases of this category is largely the same in both series (Table 1) The comparatively small number (some twenty odd in each group) does not permit any definite conclusion but on the face of it the course of the treatment appears to have been the same as described above for complicated cataracts It is worth noting also that within each group of 413 operated eyes we could not demonstrate poorer results in the diabetics than in the ordinary senile cataracts as Norn felt that he had observed in his material from 1967

Table 6

Postoperative course in complicated cases of cataract after extraction by cryotechnique or by forceps erisiphake = control series

Type of Complication	Transient corneal oedema		Corneal dystrophy		Flat ant. Chamber		Hyphaema		Iris prolapse		Secondary cataract		Cyclitic reaction		Secondary glaucoma		Phthisis		Total cases operated	
	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.	Cryo	Cont.
Sequel of iridocyclitis	7	2	1	1	6	2	12	4	0	0	2	5	6	6	0	0	1	0	39	14
Primary glaucoma	5	4	1	0	3	1	7	3	1	1	2	5	1	3	16*	10**	0	0	21	14
Dislocation of lens	0	1	0	0	2	1	0	1	0	1	1	0	0	1	0	0	0	0	11	1
Traumatic cataract	0		0		1		1		0		0		0		1		0		4	0
Retinal detachment	0	0	0	0	0	0	2	1	0	0	0	0	1	0	0	0	0	0	3	1
Excessive myopia	3	18	0	0	2	7	18	20	1	2	4	11	6	10	2	1	1	0	51	56
Total	15	25	2	1	14	11	40	29	2	4	9	21	14	20	3	1	2	0	129	85
Diabetic cataract	5	4	0	0	0	2	8	6	0	1	5	9	1	4	1	0	0	0	[illegible]	21

*) 5 cases of primary glaucoma regressing after the operation
**) 4 cases of primary glaucoma regressing after the operation

Table 7

Visual acuity obtained in complicated cases of cataract after extraction by cryotechnique or by forceps erisiphake — control series group

Type of complication	6/6 – 6/12		6/15 – 6/24		6/30 – 6/60		6/60 – 3/60		< 3/60		Total cases operated	
	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control	Cryo	Control
Sequel of iridocyclitis	17	4	13	2	4 (2 retinal deg.)	4 (2 retinal deg.)	3 (2 retinal deg.)	(1 retinal deg.)	2	2 (1 retinal deg.)	39	14
Primary glaucoma	7	7	7 (3 visual field def.)	4 (2 visual field def.)	3 (1 retinal deg.)	0	3 (1 retinal deg.)	2	1 (visual field def.)	1	21	14
Dislocation of lens	3	0	1	0	3	0	4	1	0	0	11	1
Traumatic cataract	1		1		1		1		0		4	0
Retinal detachment	0	0	0	0	1 (retinal deg.)	0	1 (still detached)	1	1 (retinal deg.)	0	3	1
Excessive myopia	28	31	14	17	7 (5 retinal deg.)	4 (4 retinal deg.)	2 (2 retinal deg.)	2 (1 retinal deg.)	0	2 (1 retinal deg.)	51	56
Total	56 45 %	42 49 %	36 28 %	23 27 %	19 14 %	8 9 %	14 11 %	8 9 %	4 2 %	5 6 %	129	85
Diabetic cataract	10	10	10 (5 retinopathy)	5 (4 retinopathy)	2 (2 retinopathy)	2 (2 retinopathy)	0	1 (1 retinopathy)	3 (3 retinopathy)	3 (3 retinopathy)	5	1

of the cornea which necessarily must arise during cryoextraction Indeed we consider endothelial damage to have been responsible for the 6 cases of corneal dysaesthesia (permanent corneal opacity) in the group treated with erisiphake or forceps compared with only one such case in the cryooperated series

In accordance with other publications on the same subject e g *Skr ɔpc ak* (19f8) we found that chymotrypsin zonulolysis was but seldom used in cryo extraction In our material we found a reduction in its use from 40 % to 26 % It should be mentioned that it was particularly during the first couple of years – i e before sufficient experience of the cryomethod had been attained – that chymotrypsin was still used as a routine We believe that the super cooled instrument causes the capsule to shrink thus creating a kind of mechanical zonulolysis" at any rate in elderly patients (*Seedorff* 1965) As a consequence of this opinion the use of chymotrypsin in our Department has been further reduced in the course of the past couple of years

The two materials also show a significant difference in respect to postopera tive cyclitic reaction which occurred more seldom in the cryoseries than in the control series This is presumably because the extraction procedure is gentler in the cryomethod

It is worth stressing also that in our cryoseries we could not demonstrate any difference in the incidence of complications according to the *maturity of* the cataract Such a difference was found in the control series where loop extrac tion was required more often in immature cataracts and where capsule *rupture* occurred more often in the more mature cataracts

Other conclusions might perhaps be deduced from the material but the numbers involved are so small that we dare *not emphasize differences* How ever it may be mentioned that postoperative prolapse of the iris occurred in only ? cases following cryoextraction – a very low incidence

In spite of significant differences in several respects – in favour of the cryo method – in the operative as well as postoperative course the end result i e the final visual acuity turns out to be al*most identical* This result is not the least interesting finding although it must be pointed out that the *cryoseries was* loaded by a larger number of complicated cases

In the *second* part of this study we investigated what *cryosurgery yields* in complicated cases of cataract As stated above the number of complicated cases is greater in the *cryoseries (129) than in the* control series (only 86) In respect to the nature of the *complications* it is apparent from the tables *for instance* that the higher percentage of sequelae of iridocyclitis as well as of dislocation of the lens were found in the *cryoseries* 39 and 11 as compared with only 14 and 1 in the control series

On this background it is remarkable *that* complications were so uncommon in the cryoseries A more *detailed statistical calculation seems* to be unnecessary to establish the superiority of the cryomethod in cataract extractions A similar

Discussion

As stated in the introduction the criteria used in the present study were as objective as possible

The premisses on which the assessment of the two series was based may seem very detailed and perhaps somewhat lengthy However we felt that we had to use such a procedure in order thoroughly to analyse differences if any between the two principles of extraction

The three most common complications of cataract surgery in general are capsule rupture loss of vitreous (including reclination) and transient or more permanent corneal damage Capsule rupture has been reduced from 30 % to 11 % after tre introduction of cryoextraction The explanation is no doubt that in the cryotechnique the super cooling gives a better grasp not only of the capsule but of the lens as a whole This wholly or partially obviates counter pressure in contradistinction to extraction by earlier methods Loss of vitreous occurred in almost 10 % of our control series, but in only 2 % of the cryooperated cases The explanation must be that in addition to a better grasp on the lens there is no need for exerting any pressure in order to grasp the capsule as for instance when using forceps Thereby the risk of dislocating the lens is practically eliminated Incidentally this view is supported by the finding that loop extraction was never required in the cryooperated material but 11 times in the control group

Corneal damage has been emphasized as an important complication to cryo extraction because of many instances of accidental contact between the instrument and the cornea As stated above such contact occurred in 15 of our cases or less than 4 % and it was in only one of these cases that serious sequelae persisted In the others the freezing to the cornea or iris left no permanent sequelae Only a transient mild corneal opacity was observed during the first postoperative days However it should be emphasized that unwanted freezing to tissues other than the lens has been considered mainly previously the chief disadvantage of the cryoextraction principle Now this risk has been considerably reduced after the advent of more advanced instruments which permit rapid heating of the tip in cases of disaster A comparison of the incidence of postoperative corneal oedema in the two materials shows that the incidence has dropped from about 24 % to 15 % after the introduction of cryotechnique It has been emphasized in the literature (*Taylor & Dalburg* 1968) that this postoperative complication is more common in *cryoextraction* either becaus the cornea has to be bent backward during the extraction or because of too common freezing of the cornea to the cooled metal This is not in keeping with our view We feel that the contact with the corneal endothelium which often occurs accidentally in procedures using e g forceps is more conducive to corneal oedema than a short lasting freezing to the cornea or the moderate kinking

of the cornea which necessarily must arise during cryoextraction Indeed we consider endothelial damage to have been responsible for the 6 cases of corneal dysaesthesia (permanent corneal opacity) in the group treated with erisiphake or forceps compared with only one such case in the cryooperated series

In accordance with other publications on the same subject e g *Skr ypc-ak* (1968) we found that chymotrypsin zonulolysis was but s-ldom used in cryo extraction In our material we found a reduction in its use from 40 % to 26 % It should be mentioned that it was particularly during the first couple of years – i e before sufficient experience of the cryomethod had been attained – that chymotrypsin was still used as a routine We believe that the super cooled instrument causes the capsule to shrink thus creating a kind of "mechanical zonulolysis at any rate in elderly patients (*Seedorff* 1965) As a consequence of this opinion the use of chymotrypsin in our Department has been further reduced in the course of the past couple of years

The two materials also show a significant difference in respect to postopera tive cyclitic reaction which occurred more seldom in the cryoseries than in the control series This is presumably because the extraction procedure is gentler in the cryomethod

It is worth stressing also that in our cryoseries we could not demonstrate any difference in the incidence of complications according to the maturity of the cataract Such a difference was found in the control series where loop extrac tion was required more often in immature cataracts and where capsule rupture occurred more often in the more mature cataracts

Other conclusions might perhaps be deduced from the material but the numbers involved are so small that we dare not emphasize differences How ever it may be mentioned that postoperative prolapse of the iris occurred in only 2 cases following cryoextraction – a very low incidence

In spite of significant differences in several respects – in favour of the cryo method – in the operative as well as postoperative course the end result i e the final visual acuity turns out to be almost identical This result is not the least interesting finding although it must be pointed out that the cryoseries was loaded by a larger number of complicated cases

In the second part of this study we investigated what cryosurgery yields in complicated cases of cataract As stated above the number of complicated cases is greater in the cryoseries (1?9) than in the control series (only 86) In respect to the nature of the complications it is apparent from the tables *for instance* that the higher percentage of sequelae of iridocyclitis as well as of dislocation of the *lens* were found in the cryoseries 39 and 11 as compared with only 14 and 1 in the control series

On this background it is remarkable that complications were *so uncommon* in the cryoseries A more detailed statistical calculation *seems to be unnecessary* to establish the superiority of the cryomethod in cataract extractions A similar

though perhaps not so marked, superiority must be attributed to the cryo technique also in the postoperative course Let us again emphasize the much lower percentage of corneal oedema and the considerably less common post operative cyclitic reaction in the cryooperated series including cases with a history of iridocyclitis

Table 7 presents the visual acuity obtained in the groups of complicated cases It is apparent as also from *Table 4 which comprised the entire series,* that in spite of more common and more serious complications in the control series the end results appear to be nearly the same In this connection how ever it must again be borne in mind that the cryoseries included a considerably larger number of cases with particularly serious complications (sequelae of iridocyclitis dislocation of the lens and traumatic cataracts)

One sequel to cataract operations has been deliberately omitted viz retinal detachment We felt unable to state our attitude to this factor with sufficient conviction because the follow up period on the operated cases is too short (cf Fig 1) It averages only about 2 years in our opinion not enough to permit a conclusion Since however the most important cause of retinal detachment *after cataract surgery is loss of vitreous one would a priori* expect a *higher* incidence of postoperative retinal detachment in the control series

The diabetic cataracts were included in the complicated cases but grouped separately as by reason of their aetiology they represent in more than one way a sign of a systemic disease

The course of the operations etc is apparent from the tables and all pre misses are according to the same pattern as described above including the end result i e the final visual acuity It should be noted that within each of the 2 × 413 operated eyes there have been no differences in the number of com plications between diabetic and non diabetic cataracts

Summary

In an eye department where all the more experienced members of the surgical staff have to be schooled in cataract surgery it is definitely easier to teach cryoextraction than the more difficult forceps or erisiphake techniques

It is moreover our experience that owing to the easier operative course with *the* cryotechnique *the operated eye is less apt to* develop either reactions during the postoperative course or later complications Consequently the patient can be discharged earlier

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HOLGER EHLERS

ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

The Eye Clinic The National Institute
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SOME EXPERIENCES WITH FLUSH FITTING SCLERAL CONTACT LENSES

BY

H SKYDSGAARD

"Ophthalmology has been slow to recognize the therapeutic potential of molded haptic lenses" *(Gould)*

However the value of haptic scleral lenses in ophthalmological therapy is now indisputable

It is the merit of *Fr Ridley* from his wide experience to have pointed out the therapeutic uses of moulded scleral contact lenses whatever may prove to be the merits of corneal lenses for cosmetic cases"

Ridley introduced a novel scleral lense called a flush fitting lense This is a direct copy of the model obtained from the impression of the eye suitably relieved but following in every detail the surface contour of both cornea and globe Such a shell is a perfect glove fit and is without doubt the most satisfactory of all from a wearing point of view

Only a capillary layer of tears separates the back surface of the lense from the irregular surface of cornea

If the posterior surface of the shell represents a perfect impression of the cornea surface a capillary layer of tears is produced and exchanged swiftly readily visible by slitlamp biomicroscope and fluorescein staining of the tears *(Girard & Soper)*

This fact has been considered essential in the *discussion of the* mechanism of the therapeutic effect of the flush fitting lens

In case of failing "glove fit adaptation the tears tend to pool and stagnate

and the therapeutic intention is thus defeated It is rightly said that the flush fitting shells are in fact an extension of ophthalmic plastic surgery and represent an alternative to conjunctival flap or tarsorrhaphy *(Gould)*
This type of shell is exclusively used in the treatment of different medicamentally intractable corneal diseases (see below) and not primarily of optical benefit In the standard optic scleral lense a space (clearance) is always present between the back surface of the lense and the corneal surface The optical power of the lens also depends on the back curve of the lens A true optical back surface of the flush fitting lens can of course not be created but if wanted some optical correction can be obtained from the anterior surface In our cases the main therapeutic problems were to eliminate subjective corneal discomfort and to heal up corneal diseases An optical effect was of secondary importance

In a paper from 1966 *Girard & Soper* have published the convincing results of flush fitting therapy in 14 cases and have listed the indications for this treatment as follows

Corneal burns corneal ulceration bullous keratitis Stevens Johnson disease neuroparalytic keratitis clouding and edema of corneal graft stromal herpes cosmetic prosthetic lagophthalmos keratitis trichiasis restoration of conjunctival fornices pemphigus keratoconjunctivitis sicca and filamentous keratitis descemetocele

In the same paper to which I should like to refer the authors give a detailed illustrated and very instructive description of the classical technique of moulding scleral lenses so an account of this procedure should not be repeated here This moulding technique has also been adopted in this clinic and has always been atraumatic to the eye Only a slight staining has sometimes been observed in connexion with the moulding The impression of the anterior segment of the eye is made of *ophthalmic tissuetex* From the mould a cast of dental stone is taken The final lense is made of acrylic plates *(Rosacrylic* a Danish product) by the pressing method advocated by *Fr Ridley* By this method the acrylic sheet is pressed over the cast and heated *Girard & Soper* prefer methyl methacrylate polymer that comes in a powder form and is polymerized

We are quite aware that a perfect replica of the cast which represents the anterior corneo scleral segment of the eye is of decisive importance It depends among other things on the caliber of the acrylic plate which is used and we try to find the optimal thickness of the shell meeting the glove fit and the wearing comfort as well At the moment the thickness is generally 0 8 mm

The total size of the shell the scleral diameter is also to be considered We readily admit that the pressing method is not ideal in all situations In most cases the shells are well adapted but sometimes a new shell must be required at once Perhaps the heating procedure should also be payed attention to when trying to obtain a better results *Possibly* the pressing method may not be the one preferred in future

The flush fitting therapy is based upon a close collaboration between ophthalmologist optician and technician

In this clinic a teamwork is easily organized because an extended low vision aid service including fitting of contact lenses is integrated in the eye clinic

In the early state of fitting the patient should be supervised daily and the perfect fit controlled by slitlamp biomicroscope and staining For this purpose we find the mixed staining fluid (fluorescein + Rosebengal) indicated by M *Norn* very useful Minor adjustments could be made in the clinic In case of persisting maladaptation which may possibly cause corneal abrasio remoulding *must be instituted and a fresh shell procured*

Even when a perfect fit has been obtained these patients should be watched constantly for weeks because the hazards of complications are still present even if a proper fit has been achieved from the beginning Later on when the condition proves to besettled the ophthalmologic controls take place at greater intervals The patients are carefully instructed how to insert remove and handle the lens

It *is beyond the scope of this paper to go into details as regards* all the clinical and technical problems of the flush fitting therapy The effectivity of this treatment cannot be questioned as emphasized by several authors Since ophthalmic publications dealing with this problem are still not very frequent and so far have not appeared in the Scandinavian literature we thought it worth while to mention some experiences in order to emphasize *the importance of this* field of ophthalmic therapy

Case histories

1 B H 22 years old male Diagnosis Buftalmia cong o u *Keratopathia bullosa dx*
Pronounced corneal complaints owing to recurring bullae pains photophobia epiphora

The minimal residual central vision and tubular field cannot be used due to continued corneal complaints in spite of intense medicamental therapy A conjunctival flap is contemplated

Insertion of flush fitting lens gives immediate comfort but there is unmistakable discomfort when lens is removed Recurring complaints and fitting difficulties result in remoulding and a new lens

After a few months almost constant well being is reported have not been so well for the last 1½ years Wearing time increases up to 2 months No bullae Perfect fit

At ophthalmologic control the lens is cleansed by *the ultrasonic methods* (Bandelin Sonorex) and swiftly inserted as there is still some subjective discomfort after removal of lens

After one year longest uninterrupted wearing time *15 weeks There is* subjective well being and satisfaction Adaptation ideal No bullae Very slight debris behind the

lens Instillation of pilocarpine four times daily Tension is regulated at 10 mm The latest examination showed no staining of the cornea and there were no complaints at removal of lens

2 G O 73 year old female Diagnosis Myopia excessiva Keratitis parenchymatosa (luic) seq Transplantatio lamellaris corneae dxt facta *Aphakia postop o dxt Keratopathia bullosa o dxt*

During a period of 1½ years recurring bullous keratopathy has been treated medicamentally The epithelium has been removed several times without lasting improvement of the considerable subjective complaints (pains and epiphora) Another graft is considered for therapeutic reasons Visual acuity 0 3/60

The subjective complaints cease immediately after insertion of a flush fitting lens Good adaptation No bullae Patient feels discomfort when the lens is removed and the eye is immediately ciliary injected Slightly increasing clearing up of the corneal opacities

After transitory ocular irritation there is constant well being The lens is removed and cleansed every other day No staining The lens has been used for 22 months with no complaints

3 T N 47 year old female Diagnosis Leucoma corneae (corrosionis seq) *Keratitis epithelialis recidivans*

Numerous recurrencies of keratitis with strong subjective complaints for about 14 months No lasting effect of intensive medicamental treatment Conjunctival flap or tarsorraphy considered Not motivated for keratoplasty

Moulding and insertion of flush fitting lens gives immediate relief

Uninterrupted wearing time increases up to 8 10 days but remoulding necessary after 1 month The new lens is well adapted good tolerance Subjective satisfaction The eye settles and the corneal opacities are slightly clearing up There is transitory discharge (wetting solution?) Patient prefers daily removal and rinsing of lens She is still well and states that she gets pains in her eye when the flush fitting lens is removed only for a few minutes Very slight Rose Bengal staining of cornea

The lens gradually becomes mobile (change of corneal surface) with slight debris behind lens After 11 months the wearing time is scaled down After about 1 year the initial complaints have completly disappeared and flush fitting therapy must be considered concluded

One year later the patient complains of tendency to photophobia and epiphora but no pain Later lamellar corneal graft is carried out following a pre operative strontium treatment for massive vascularization

4 S B 61 year old male Diagnosis *Keratitis herpetica o dxt Ulcus corneae o dxt*

Since age ten patient has suffered from recurring keratitis has consulted the oculist all my life Almost constant symptoms in right eye During the last months there have been severe recurrencies decreasing vision pains and photophobia No lasting effect after prolonged local medicamental treatment including caustics The right cornea is opaque oedematous with a deep ulceration Sensitivity is considerably reduced

Flush fitting lens is inserted with good adaptation and only little subjective complaint After about 4 weeks severe purulent discharge so the lens is removed for one month Antibiotic treatment Upon reinsertion no complaints good tolerance and wearing time increases from 2 to 24 days

New lenses after repeated mouldings give no better fit than the primary lens, which adapts satisfactorily After 6 months the lens can be worn for three weeks without removal and after 15 months the wearing time is increased to 11 weeks Generally no symptoms eye is quiet only *slight Rose Bengal staining on cornea* The corneal ulcer is healed Considerable vascularization develops and corneal graft is considered too hazardous When lens is removed for eye control there is some irritation and subjective complaints These discomforts disappear gradually after reinsertion of lens which has been worn for 17 months

5 T C 48 year old female Diagnosis *Keratitis neuroparalytic o sin (anæsthesia corneæ)* neurinomae n acustici sin operat seq lagoftalmus et tarsorraphiae seq cataracta immatura

Since surgery for acustic neurinoma there has been recurring irritation and injection in the left eye No relief after prolonged local treatment Pronounced staining with *Rose Bengal (not with fluorescein) Insertion of flush fitting lens due to considerable* corneal complaints Good adaptation The subjective complaints decrease immediately Tolerance of about 2 days is swiftly achieved

Remouldings are made after 1 4 and 10 months presumably due to alterations of the corneal surface The lens becomes mobile and maladapted and air bubbles are seen behind the lens

After insertion of a fourth lens severe keratoconjunctivitis occurs It is treated with antibiotics locally and orally After 6 weeks eye is absolutely quiet and lens is reinserted The eye remains quiet During the next half year the lens is worn without complaint or dissatisfaction The lens is removed and rinsed every eight day

Last examination revealed no injection of the eye lens well adapted

There is very slight debris scattered Rose Bengal staining and traces of fluorescein staining

6 E S 50 year old male Diagnosis Aphakia postop o dxt *keratoconjunctivitis sicca*

Succesful correction of unilateral aphakia using both corneal and scleral optic lenses has earlier failed owing to a sicca syndrome

Flush fitting lens is inserted and on the whole patient accepts is The considerable debris behind the lens decreases gradually Intermittent complaints (small central abrasio) During 4 weeks however wearing time increases up to 8 days

As the sicca complaints disappear a + 13 0 optic lens is provided from the same cast After 12 days use is discontinued for one week due to an abrasio and bulbar irritation *Local treatment administered Considerable* filamentous elements reoccur After remoulding an optic lens is inserted again

This lens is accepted with moderate complaints detritus decreases Patient is able to rinse lens himself Wearing time and visual acuity vary After 6 months wearing time is normally 2 days After 10 months there are *still no sicca complaints* have never been so well as during the last 2 months Has full working capacity as a clerk and would not do without the lens in spite of intermittent irritation (treated with antibiotics)

Latest slit lamp control revealed no fluorescein staining *The proper flush fitting* therapy in this case probably should have been extended for a longer period before an optic lens was provided

7 H H 43 year old male Diagnosis *Dystrophia corneae* cause unknown *(possibly* toxic)

Primary fitting of an optic scleral lens to the left eye resulted in considerable improvement of vision but without succes from a wearing point of view An epithelial defect has appeared After local treatment a flush fitting lens is inserted with good adaptation Wearing time up to 48 hours

After one month corneal reactions and possibly non ophthalmological factors prevent further flush fitting theraty for the present

We have furthermore started flush fitting lens therapy in two cases which both appear to be succesfull

8 N W 38 year old female Diagnosis Aniridia cong *Keratitid seq Dystrofia epithelialis corneae*

9 E C 75 year old female Diagnosis Myopia excessiva *Aphakia postop dxt Keratopathia bullosa dx*

Comments and Summary

In six probably eight cases application of a flush fitting lens has proved to be a valuable therapeutic measure superior to medicamental or surgical treatment In all eight cases the therapy was preceded by a long period of severe corneal complaints which had caused an intolerable situation for the patient

Though in two cases (4 5) the therapeutic course has been complicated by severe intercurrent inflammations the final results were absolutely beneficial but these events emphasize the importance of watching the patients closely as allready mentioned The patients are told to call at the clinic immediately if local ocular discomfort should arise

The immediate relief in most cases is remarkable Usually a tolerance of two or several days is quickly obtained but the final unbroken wearing time has varied Some patients want to have the lens taken out and cleansed every other day or every week while two patients (1 4) have had an unbroken wearing time of 11 15 weeks These variations are not dependant on the actual corneal disease Remoulding has been made in nearly all cases but the final lens can be worn for months It is to be considered that during the course of healing the surface contour of cornea may change This necessitates a new shell

It is a noticeable feature that on removal of the lens some patients felt immediate ocular discomfort while the eye was slightly injected These inconveniences disappeared after reinsertion

We have seen no manifestations of acrylic idiosyncrasy

It should finally be mentioned that by long term use of a lens crystalline deposits on the anterior surface of the lens can be observed These are easily removed by ultrasonic cleansing – The flush fitting lens treatment is a valuable

adjunct in a difficult field of ophthalmic therapy The cases reported in this paper represent only a few therepeutic possibilities In all our patients it is a matter of chronic or subchronic corneal diseases but among a variety of indications I should like to call particular attention to the striking effect in cases of severe alkali burns of the eye as published by *Girard & Soper*

In the future no doubt, this kind of therapy will be increasingly employed within the field of indications listed above

Acknowledgement

I am greatly indebted to W Triang senior optician and his assistant optician, mrs B Kristensen for their enthusiasm and valuable collaboration

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From the Eye Clinic
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(Chief H Skydsgaard M D)

EYE IMMOBILISER FOR SLIT LAMP EXAMINATION OF PATIENTS WITH NYSTAGMUS

A New Instrument

BY

METTE WARBURG

Slit lamp examination of a patient with nystagmus is often difficult Even if the patient can restrain the nystagmus by extreme lateral gaze it is usually impossible to inspect the eye from more than one angle Immobilisation and rotation of the eye by a forceps require the use of a potent topical anaesthetic such as repeated instillations of cocaine and local application of a cotton wool swab with a 10% cocaine solution Extensive subconjunctival haemorrhages are always produced Children usually object to this examination – and so do their mothers even more energetically Accordingly in patients with nystagmus it is often difficult without general anaesthesia, to plan corneal grafting in cases of leukoma or to examine a congenital or secondary cataract in order to decide if a discission should be performed If intra ocular inflammation develops in a patient with nystagmus the Tyndall phenomenon is difficult to follow and it is also difficult to remove foreign bodies from the cornea It is often impossible to take an external or retinal photograph when rapid nystagmus is present.

In my work at the Eye Clinic for the Blind and Partially Sighted I have felt the need for an instrument which can immobilise the eye in a patient sitting in front of the slit lamp or a camera and I have therefore devised a haptic plastic eye immobiliser mounted on a handle (Fig 1) The corneal part of the device

adjunct in a difficult field of ophthalmic therapy The cases reported in this paper represent only a few therepeutic possibilities In all our patients it is a matter of chronic or subchronic corneal diseases but among a variety of indications I should like to call particular attention to the striking effect in cases of severe alkali burns of the eye as published by *Girard & Soper*

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If desired the immobiliser can be manufactured in other sizes according to specification The largest of the three sizes can be used for examination of most *hydrophthalmic eyes* The dimensions are shown on the scleral part of the device It can be cleaned in the solution used for cleaning the applanation tono meter (Merfen® phenylmercuric borate) The instrument should not be used during applanation tonometry or Schiotz tonometry because the pressure needed for immobilisation of the eye will give faulty readings

The Hruby lens may be used for ophthalmoscopy together with the immobili ser but instead of using the immobiliser I prefer to do ophthalmoscopy on pa tients with nystagmus through Goldman s three mirror lens When this lens is placed on the cornea the nystagmus can be almost completely eliminated and all parts of the retina and the posterior parts of the vitreous can be examined in the usual way The three mirror lens is an important tool in the differential diagnosis of malformations leading to secondary and congenital nystagmus The posterior pole may be visualised with the smaller one mirror gonio lens in young children and with Richardson s lens in infants

With these devices congenital aberrations such as aplasia of the macula incipient macular pigmentations the retinopathy of foetal rubella and con genital malformations of the optic nerve are easily diagnosed and it is often possible to inspect the retina through a small aperture in a secondary cataract because the eye is immobilised



Fig 1
Plastic eye immobiliser Due to the illumination during photography the instrument appears opaque

is cut away and only the haptic part remains The immobiliser can be placed direct on the eye after instillation of a mild topical anaesthetic (Novesin® 2 %) and by pressing gently backwards the nystagmus is arrested The eye can be rotated in the directions desired, and foreign bodies can be removed from the cornea through the aperture of the immobiliser With the patient in the sitting position the eye can be immobilised while an external or retinal photograph is taken (Fig 2)

The device is manufactured *) in three different sizes of the following dimensions

Diameter of corneal aperture (mm)	Scleral radius (mm)	Over all diameter (mm)
10	12	22
11	13	23
12	14	24



Fig 2
The eye immobiliser *in situ* The transparency of the device is evident The instrument immobilises nystagmus in a case of aniridia

*) The eye immobiliser is manufactured by C I Optik Pinievej Copenhagen Denmark

pressure was elevated All patients were given rest in bed but not completely for three to four days He observed that greater freedom of movement did not increase the number of complications and that the use of cortisone and mydriatics prevented secondary iritis and secondary haemorrhage

This paper reports the results of an investigation which was carried out to find out whether there was a relationship between the ultimate therapeutic results the time patients with contusion of the eye have to be treated in hospital and the method of treatment used

Method of Treatment and Case Material

From September 1967 to September 1968 117 patients with contusion of the eye were treated as in patients in the Eye Clinic Karolinska Sjukhuset The condition was caused by blunt injury in all cases None of these patients showed any signs of perforation of the eyeball

Two types of treatment were given *i e* one patient received one type of treatment and the next in order of sequence in which he was admitted to hospital the other type Thus the patients were classified into two groups by the type of treatment given and in the order of sequence they were admitted to hospital and not by the degree of severity of the injury to the eye

The patients in Group I received the usual conservative treatment *i e* complete rest in bed without the use of pinhole spectacles or simultaneous local therapy The patients in Group II were allowed to wear their clothes and to move about freely in the hospital ward but they were instructed to avoid vehement movements of the body Their treatment consisted in the local application of atropin once daily with simultaneous Decadron eye drops to the injured eye five times daily beginning this therapy on the day of their admission to the Clinic Eight patients in this group showed erosion of the cornea For this reason 5 of them did not receive this treatment until the second and the other 3 patients not until the third day after their admission to hospital In a few patients there was a rise in intra ocular pressure while they were on the above therapy They were therefore given either Diamox alone or they were operated on or Diamox therapy was combined with surgery These cases are discussed in more detail below

Table I shows the average age of the patients the average visual acuity and average intra ocular pressure in the injured eye as determined on their admission and discharge the average height of the existent hyphaema the number of cases in which abnormalities of the pupil co existed in the injured eye and the number of days they were treated as in patients

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ANNIS LXX FELICITER EXACTIS DEDICATUM DIE XXX MAII MCMLXIX

From the Eye Clinic
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THE TREATMENT OF CONTUSION OF THE EYE

BY

BIRGITTA ZETTERSTRÖM

Contusion of the eye is relatively common As patients with this injury may require treatment in hospital for quite a number of days they often occupy a considerable portion of the bed space available in an eye clinic

The treatment given to in patients varies greatly Some workers advocate complete rest in bed possibly with the simultaneous use of pinhole spectacles but without simultaneous medical treatment (*Duke Elder* 1954 *Shea* 1957 *Henry* 1960 *Gregersen* 1962) According to others air should be blown into the anterior chamber of the eye to prevent secondary haemorrhage (*Wilson McKee Campbell* and *Miller* 1954) *Rychener* (1944) *Smith* (1952) *O Neill* (1952) recommend the use of miotics whilst *Laughlin* (1948) *Lock* (1950) *Thygeson* and *Beard* (1952) *Hogan* (1952) and *Loring* (1958) prefer the use of mydriatics The administration of corticosteroids at an early stage has also been recommended *Whitwell* (1959) applied corticosteroids locally and systemically *Benedict* and *Hollenhorst* (1953) working with contusions of the eye in rats observed that cortisone retards the absorption of a hyphaema *Oksala* (1967) reported 118 cases of post traumatic hyphaema encountered in the years 1961 to 1964 He based the choice of the method of treatment on the degree of severity of the haemorrhage into the anterior chamber of the eye in the presence of a small hyphaema he applied mydriatics locally with simultaneous cortisone eye drops if it was large he administered mydriatics alone and if it was very large he did not give any local treatment at all unless the intra ocular

pressure was elevated All patients were given rest in bed but not completely for three to four days He observed that greater freedom of movement did not increase the number of complications and that the use of cortisone and mydriatics prevented secondary iritis and secondary haemorrhage

This paper reports the results of an investigation which was carried out to find out whether there was a relationship between the ultimate therapeutic results the time patients with contusion of the eye have to be treated in hospital and the method of treatment used

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The patients in Group I received the usual conservative treatment *i e* complete rest in bed without the use of pinhole spectacles or *simultaneous local* therapy The patients in Group II were allowed to wear their clothes and to move about freely in the hospital ward but they were instructed to avoid vehement movements of the body Their treatment consisted in the local application of atropin once daily with simultaneous Decadron eye drops to the *injured* eye five *times daily* beginning this therapy on the day of their admission to the Clinic Eight patients in this group showed *erosion* of the cornea For this reason 5 of them did not receive this treatment until the second and the other 3 patients not until the third day after their admission to hospital In a few patients there was a *rise in* intra ocular pressure while they *were on the* above therapy They were therefore *given either* Diamox alone or they were operated *or* Diamox therapy was combined with surgery These cases are discussed in more detail below

Table I shows the average age of the patients the average *visual acuity* and average intra ocular pressure in the *injured eye as* determined on their admission and discharge the average height of the existent hyphaema the number of cases in which abnormalities *of the pupil* co existed in the injured eye and the number of days they were treated as in patients

Table I

Groups I and II Age of patients findings and length of treatment in hospital

	No of cases	Average age years	Average VA* on admission	Average VA on discharge	Average IOP** on admission mm	Average IOP on discharge mm	Average height of hyphaema mm	Co existent abnormalities of the pupil No of cases	Treatment time days
Group I	59	20 4	0 51	0 91	17 2	12 9	3 5	34	8 9
Group II	58	23 6	0 52	0 96	16 2	14 1	2 5	36	5 9

*VA visual acuity
**IOP intra ocular pressure

Group I included 59 patients treated conservatively *i e* with complete rest in bed but without applying local therapy simultaneously Nine of these patients were women and 52 were men Their average age was 20 4 years (Table I) the majority being in the age group 10 to 20 years The youngest patient was 5 and the oldest was 56 years old (Table I)

Group II comprised 58 patients who were allowed to move about freely in the hospital ward and who received atropin with simultaneous Decadron eye drops Eight of these patients were women and 50 were men Their average age was 23 6 years the majority being in the age group 10 to 20 years also in this group The youngest patient was six and the oldest was 57 years old (Table I)

The visual acuity in the injured eye was on average 0 51 on admission of the patients in Group I that of the patients in Group II being on average 0.52 Thus the degree of visual deterioration as recorded on admission of the patients was virtually the same in the two groups of unselected cases (Table I)

In order to be able to a sess the effect on intra ocular pressure of the two methods of treatment discussed the intra ocular pressure in the injured eye was determined on admission of the patients being in Group I on average 17 2 mm and in Group II 16 2 mm (Table I)

In the cases in which hyphaema was present its height was measured on admission of the patients being on average 3 5 mm in Group I and 2 5 mm *in Group* II (Table I) The patients in either group were treated as in patients until the visual acuity in the injured eye was satisfactory the hyphaema was absorbed and the intra ocular pressure did not appreciably deviate *from* the normal

Following the above criteria the patients in Group I were treated as in patients on average 8 9 days the corresponding figure in Group II being 5 9 days (Table I)

Naturally the degree of visual acuity could not be used as *criterion for* discharging the patients in the cases of severe *injury to the* eye such as traumatic cataract dislocation of the lens and damage to the optic nerve

Table I shows that the intra ocular pressure in the injured eye was on average lower (16 2 mm) on admission of the patients *in* Group II as compared to the average intra ocular pressure (17 2 mm) in the cases in Group I on admission of the patients whilst on discharge of the patients *in Group* I it was on average lower (1. 9 mm) than in the cases in Group II (14 1 *mm*)

As the possibility could not b excluded that the cases of severe injury to the eye which required prolonged treatment in hospital (Table II) might bias the figures of the average length of the patient s stay in hospital the cases in which the patient was in hospital *for more* than 10 days were excluded Thereafter the avera e duration of the other patients stay in hospital *i e* of those who were treated as in patients for *less than 10* days was determined in either

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group It was found that the patients in Group I were treated in hospital on average for 6 3 days the corresponding figure in Group II being 4 8 days

The cases of severe injury to the eye excluded from Group I numbered 8 those excluded from Group II numbering 5 Table II shows the type of injury present on admission of these patients their age and the number of days they were treated in hospital

A study of the intra ocular pressure in the injured eye in the cases in Group I as recorded during the patients stay in hospital showed that it was elevated in 2 cases In one of these cases there was dislocation of the lens and secondary haemorrhage into the anterior chamber of the eye surgery paracentesis followed by cyclodialysis and Diamox therapy resulted in controlling the high intra ocular pressure In the other there was secondary haemorrhage decompression being achieved by paracentesis and Diamox therapy Five patients in this group had hypotension of less than 10 mm during their stay in hospital

In Group II the intra ocular pressure was elevated in 3 cases In two of these

Table II

Groups I and II Complications age of patients and treatment time

	Complications	No of cases	Age years	Treatment time days
Group I	Secondary cataract	1	7	22
	Retinal tear	2	9	23
			31	19
	Secondary haemorrhage into the anterior chamber of the eye	4	12	19
			11	22
			11	12
			20	12
	Dislocation of lens + secondary rise in intra ocular pressure	1	56	40
Group II	Damage to the optic nerve	1	41	15
	Oedema of retina	2	56	15
			42	11
	Secondary rise in intra ocular pressure	2	32	12
			34	16

decompression was achieved by discontinuing the application of atropin and cortisone eye drops and in the other by discontinuing this treatment and giving Diamox instead It should be mentioned however that the rise in intra ocular pressure had occurred on the second and third day respectively of these patients stay in hospital at a time when the hyphaema was completely absorbed in 2 patients and was $1/8$ mm high in the third This excluded the possibility of a new haemorrhage into the anterior chamber of the eye being the cause of the rise in intra ocular pressure In a further 2 cases in this group there was hypotension of less than 10 mm

The average visual acuity in the 59 cases in Group I was 0 91 on admission of the patients (Table I) In 53 of them it was 0 7 or more on discharge of the patients and in the other 6 cases it was less than 0 7 traumatic cataract (2 cases) extensive oedema of the retina (1 case) dislocation of the lens (1 case) blood staining of the cornea (1 case) and a macula hole (1 case) being the causes of the deterioration of visual acuity Of the 58 patients in Group II whose visual acuity was on average 0 96 on their discharge the average visual acuity was 0 9 or more in 56 patients on their discharge In the other 2 cases it was less than 0 9 the deterioration being due to atrophy of the optic nerve in one of them and dislocation of the lens in the other

Discussion

The present investigation has shown that the prognosis is good in cases of contusion of the eye at least the immediate prognosis This appears to be true no matter which of the two methods of treatment discussed is used The healing of the injury took a more favourable course in the patients in Group II inas much as the ultimate visual acuity was on average virtually the same as that in the cases in Group I and their stay in hospital on average about three days shorter If the cases of severe injury to the eye (Table II) are excluded from either group their stay in hospital was about 1 5 days shorter It is interesting to note that of the 59 patients in Group I 11 patients showed symptoms of mild secondary iritis on their discharge despite the fact that *their visual acuity was* satisfactory the hyphaema was absorbed and the intra ocular pressure was normal For this reason they received further treatment as out patients which consisted in local atropin with simultaneous decadron eye drops The patients in Group II did not show any symptoms of secondary iritis on their discharge

Table I shows that the intra ocular pressure in the injured eye in the cases in Group II was on average higher than in Group I but did not exceed its normal level The 5 cases in Group II in which a rise in intra ocular pressure

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occurred on the second and third day of the patients stay in hospital and decompression was achieved by *discontinuing the administration of* atropin and Decadron eye drops, are of interest Haemorrhage into the anterior chamber of the eye cannot have caused the rise in intra ocular pressure as the hyphaema was completely absorbed in 2 of these cases and was only 1/2 mm high in the third Cortisone which may cause a rise in intra ocular pressure can hardly have been a causative factor as the patients were treated with this drug only for two and three days respectively It is more likely that the effect of atropin on a swollen iris may have contributed to a temporary blockade in the angle of the chamber of the eye despite the fact that the depth of the latter was normal This leads one to assume that the simultaneous application of atropin and cortisone eye drops is indicated only in cases in which the patient shows symptoms of secondary iritis In cases with no signs of iritis one might discontinue all local treatment or possible give only topical cortisone, allowing such patients to move about freely in the hospital ward Another method of choice is to treat such patients as out patients provided that their domestic environment permits treatment in the home follow up examinations at regular intervals are then imperative

Summary

One hundred and seventeen unselected cases of contusion of the eye were divided into two groups according to the method of treatment used The patients in one group were given rest in bed alone and those in the other received local atropin with simultaneous cortisone eye drops and were allowed to move about freely in the hospital ward The ultimate therapeutic results are reported and evaluated

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Race (*Gradle & Sugar* 1940 and 1947 *Tarkkanen* 1962 *Lowe* 1964) milieu (sunshine) (*Ørgen* 1949 *Zlatar* 1965) and nutritional factors (*Tarkkanen* 1962 *Zlatar* 1965) are suggested as possible explanations for these differences in incidence Several authors have shown familial occurrence of fibrillopathy (*Gifford* 1957 *Tarkkanen* 1962 and 1965 *Amalric Sampaolesi & Bessau* 1960 *Bertelsen* 1965 *Sæbo* 1961)

However fibrillopathy occurs all over the world and there is no obvious reason for great variation in its distribution The considerable differences in incidence are perhaps merely apparent (*Bertelsen* 1966 a 1966 b) In Denmark and Sweden for instance some ophthalmologists earlier thought that fibrillopathy was rare but recent investigations however show frequencies very similar to those found in Norway (*Strömberg* 1962 *Ladekarl* 1965 *Backhaus & Lorentzen* 1966 *Brændstrup* 1966)

The explanation of the difference in various studies perhaps lies in factors which may influence the results such as selection of population age and sex distribution of those examined examination conditions accuracy of examination and not least the ophthalmologist s interest in fibrillopathy

These factors may possibly be of such importance that many of the materials cannot be directly compared

The purpose of this study was to investigate whether there is any basis for maintaining the common view that there is conciderable variation in the geographic distribution of fibrillopathia epitheliocapsularis This study is based on personal investigations in Norway where fibrillopathy seems to be very frequent (*Horven E* 1935 *Holst* 1947 *Thomassen* 1949 *Petersen* 1958) and in England and Germany where earlier studies indicate a very low incidence (*Handmann* 1926 *Blaickner* 1937 *Butler* 1938 *Garrow* 1938 *Thomassen* 1949 *Jones* 1951 *Leydhecker* 1960 *Hollows & Graham* 1966)

Material

All persons included in this study were examined by the author The same slit lamp (Haag Streit 900) was used in temporary dark rooms at the various examination places in order to make examination conditions as comparable as possible Persons with previously diagnosed glaucoma were excluded and also those with changes which made it impossible to see the lens surface clearly (e g maculae corneae membranous exudate following inflammation etc) All persons over 60 years of age at the investigation centres were asked to attend

In Norway the material was collected in Bergen in 1962 by investigation at 30 different homes for the aged 766 persons over 60 years were examined be

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From the University of Bergen School of Medicine
Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)

THE GEOGRAPHICAL DISTRIBUTION OF FIBRILLOPATHIA EPITHELIOCAPSULARIS

so-called senil exfoliation or pseudoexfoliation of the anterior lens capsule

BY

HENRY AASVED

Fibrillopathia epitheliocapsularis is a new name for the condition best known under the name of "senile exfoliation (*Vogt* 1931) or pseudoexfoliation (*Dvorak-Theobald* 1954) of the anterior lens capsule The new term was proposed on the basis of microscopic and electron microscopic examinations of the lens capsule and lens epithelium (*Bertelsen Drablos & Flood* 1964) This descriptive term will be used in this article often abbreviated to fibrillopathy

It is a common view that the frequency of fibrillopathia epitheliocapsularis varies from place to place (*Gradle & Sugar* 1940 and 1947 *Thomassen* 1949 *Holm-Pedersen* 1952 and 1954 *Sunde* 1956 *Duke Elder* 1957 *Evans* 1951 *Gifford* 1957 *Holmes* 1957 *Paufique & Audibert* 1958 *Leydhecker* 1960 *Joannides & al* 1961 *Tarkkanen* 1962 *Clements* 1968) This view is mostly based on materials collected from eye specialist practices ophthalmological outpatient clinics or among patients admitted to eye departments There are also a few investigations from old people s homes and from the general population These earlier works are surveyed in tables 1 and 2

Table 1 covers materials which also include incidental glaucoma patients The materials in table 2 cover only persons with glaucoma Both tables show a considerable difference in the incidence of fibrillopathy from country to country and also within the same country

Race (*Gradle & Sugar* 1940 and 1947 *Tarkkanen* 1962 *Lowe* 1964) milieu (sunshine) (*Orgen* 1949 *Zlatar* 1965) and nutritional factors (*Tarkkanen* 1962 *Zlatar* 1965) are suggested as possible explanations for these differences in incidence Several authors have shown familial occurrence of fibrillopathy (*Gifford* 1951 *Tarkkanen* 1962 and 1965 *Amalric Sampaolesi & Bessau* 1960 *Bertelsen* 1965 *Sæbø* 1967)

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Table 1

Incidence of fibrillopathy in different countries in earlier investigations

Country	Author	Year	Selection	Age	No investigated	Persons with fibrillopathy	
						No	Per cent of investigated
Chile	Bitran & Villalobos	1959	Persons in old people s home	60 99	100	7	7
Denmark	Ladekarl	1965	Persons in old people s homes out patients cataract patients in hospital				
				Over 60	800	17	2 1
	Backhaus & Lorentzen	1966	Hospital patients without glaucoma				
				35 100	404	4	1
Egypt	Maghraby	1937	New cases in eye hospital				
				All ages	18 000	19	0 1
England	Jones	1957	Cataract patients				
				Over 48	333	4	1 2
	Hollows & Graham	1966	Population study				
				40 75	4231	10	0 2
Finland	Lindberg	1917	Normal patients in eye specialist practice				
				50 76	60	4	7
	Lindberg	1917	Cataract patients in eye specialist practice				
				40 78	142	28	20
	Kaivonen	1961	Patients in eye specialist practice				
				Over 60	~ 600	63	10
(Aland Islands)	Forsius & Eriksson	1961	Population study				
				Over 40	222	19	8 5
France	Paufique & Audibert	1958	Cataract patients				
				Over 60	750	27	3 5
Greece	Trantas	1929	Patients in eye specialist practice				
				55 80	237	36	1
	Trantas	1934	Patients in eye specialist practice				
				Over 0	844 eyes	112 eye	13 3

	J n ' s & al	1961	O t p t nt	C0 9	1530	149	10
Ind	Irvine	1940	Cat ract pat ents	Elderly	235	18	8
	S o l	1968	Out patients	50 J0	2139	40	19
Italia	Busacca	19 8	Cataract patients	Over 60	97	7	26
	Baumgart	1933	Hospital patients	Over 50	611	46	75
	Travi & al	1948	?	Over 5?	80	6	75
	Grignolo & Cambiaggi	1957	Cataract patients	Elderly	337	92	6
	Grignolo & Cambiaggi	1961		Unknown	1903	69	33
Jugoslavia	Zlatar	1965	New hospital patients	?	6035	52	1
Norway	Gjessing	1990	Patients in eye specialist practice	Over 60	106	3	2
	Horven E	1935	Persons in old people s home	50 90	69	4	6
	Horven E	1935	Out patients and hospital patients	60 100	30	5	17
	Horven E	1935	Cataract patients	50 90	55	10	18
	Horven E	1935	Post mortem material	50 90	34 eyes	1 eye	3
	Bertelsen & al	1965	Industrial investigation	50 70	618	6	1
	Klouman	1967	Patients in eye specialist practice	Over 60	1491	109	76
	Larsen	1968	*Post mortem* material	Over 70	50	6	12
Russia	Pletneva	1928	?		58		53
	Hoorgina	1979	?	advanced	100	48	48
Switzerland	Lehsteiner	19 9	Persons from 7 old people s homes	Over 60	938	4	2
Turkey	Ørgen	1949	?	Over 50			189
U S A	Irvine	1940	950 cataract patients 96 glaucoma patients	Over 50	2,6	8	3

Table 2
Frequency of fibrillopathy in patients with glaucoma

Country	Author	Year of publication	No patients with glaucoma	Patient with fibrillopathy		Comments
				No	Per cent	
Argentine	Sampaolesi	1960	Not given		14	
	Maggi Zawalia & Ferrero	1950	54	24	44	
Australia	Gillies	1962	88	19	21 5	Out patients
Denmark	Ladekarl	1965	31	8	26	Out patients & hospital patients
England	Thomassen	1949	50 eyes	1 case	2 (4?)	
	Jones	1957	128	7	5 5	
	Hollows & Graham	1966	20	0	0	13 patients with glaucoma simplex 7 with low tension glaucoma in a population study
(Isle of Man)	Clements	1968	43	21	49	Hospital patients
Finland	Lindberg	1917	60	30	50	Out patients
	Kaivonen	1961	161	38	24	Eye specialist practice
(Aland Islands)	Forsius & Eriksson	1961	7	4	57	Patients from population study
Germany	Blaickner	1932	84	5	6	
	Leydhecker	1960	[illegible]00 eyes	0	0	
Greece	Trantas	1934	149 eyes	68 eyes	46 6	Eye specialist practice
	Joannides & al	1961	420	16[illegible]	39 5	178 operated iridencleisis
	Joannides & al	1961	145	60	41	Out patients
India	Irvine	1940	33	8	24	Hospital patient
	S[illegible]	1968	71	13	18	Out patient

Ita y	Busacca	19 8	38	93	60	Out patients & hospital patients
	Baumgart	1933	39	99	49	Hospital patients
	Travi & *al*	1948	?	?	15 5	
	Grignolo & *Cambiaggi*	1957	90	18	90	
	Grignolo & Cambiaggi	1961	*154*	27	17 5	
Japan	Ogino Kawata & Yutaka	1963			10 6	
New Zealand	Wilson	1953			18	Out patients
Norway	Malling	1973	81 eyes	33 eyes	41	I ye specialist practice
	Horven I	*1935*	130	108	85	Hospital patients operated
	Horven L	*1935*	43	40	93	Hospital patients
	Holst	*194*	459	375	82	Hospital patients
	Thomassen	*1949*	33	31	79	Hospital patients
	Jetersen	*1953*	195	150	77	Hospital patients
	Bertelsen & al	*1965*	15	5	90	Industrial investigation
Russia	Musabejli	*1950*	114 eyes		34	
Scotland	Garrow	*1938*	51	8	16	Eye specialist practice
Sweden	Stromberg	*1962*	913	97	10	Persons with intracolar pressure of *5 9/7 5 or* higher *(Schio) in ma s* screening
Switzerland	*Vogt*	1930	*150*	13	8 6	
U S A	*Irvine*	1940	*195*	5	4	Hospital patients (Dilated pupils in 26)
	Gradle & Sugar	1940	*275*	37	13 5	Hospital patients
	Gradle & Sugar	1947	*377*	46	12	Hospital patients
	Lemoine	1950	816	99	4	Hospital patients
	Horven I	1966	100	98	28	Out patients

Table 2

Frequency of fibrillopathy in patients with glaucoma

Country	Author	Year of publication	No patients with glaucoma	Patient with fibrillopathy		Comments
				No	Per cent	
Argentine	Sampaolesi	1960	Not given		14	
	Maggi Zawalia & Ferrero	1950	54	24	44	
Australia	Gillies	1962	88	19	21 5	Out patients
Denmark	Ladekarl	1965	31	8	26	Out patients & hospital patients
England	Thomassen	1949	50 eyes	1 case	2 (4?)	
	Jones	1957	128	7	5 5	
	Hollows & Graham	1966	20	0	0	13 patients with glaucoma simplex 7 with low tension glaucoma in a population study
(Isle of Man)	Clements	1968	43	21	49	Hospital patients
Finland	Lindberg	1917	60	30	50	Out patients
	Kaivonen	1961	161	38	24	Eye specialist practice
(Åland Islands)	Forsius & Eriksson	1961	7	4	57	Patients from population study
Germany	Blaickner	1932	84	5	6	
	Leydhecker	1960	500 eyes	0	0	
Greece	Trantas	1934	149 eyes	68 eyes	46 6	Eye specialist practice
	Joannides & al	1961	420	165	39 5	178 operated iridencleisis
	Joannides & al	19[illegible]1	145	60	41.[illegible]	Out patients
India	Irvine	1940	33	9	24	Hospital patients
	S[illegible]	1968	71	15	18	Out patient

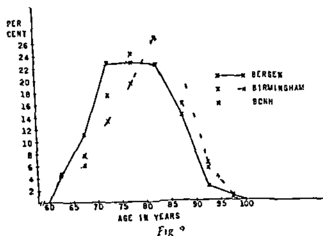


Fig 2
The age distribution in 5 year age groups of women

years all examined after instilling drops of *Mydriaticum* (Roche) The attendence here varied from 40 to 80 % of the inmates of the homes

The sex distribution in the three materials is shown in table 3

Relatively few men were examined as there were far more women than men living at the old people s homes

The age distribution in 5 year groups of men and women is illustrated in figs 1 and 2

Results

The incidence of fibrillopathy among those examined is shown in tables 4 5 and 6 The frequency is given for 10 year age groups and for all ages combined

In Birmingham the frequency of fibrillopathy among men was 2 7 % increasing from 0 % in the age group 60 69 to 7 7 % in the age group 90 99 years In the Bonn material the total frequency was 7 7 % and in Bergen 3 3 % Both the latter places showed much the same frequency in the various age groups In the total number of men examined the incidence of fibrillopathy was 3 7 %

Among women there is a tendency to increased frequency of fibrillopathy with increasing age in all three investigation places In Bergen the total incidence was / 4 % in Birmingham 4 8 % and in Bonn 4 0 % The total for all the women examined was 5 6 %

Table 3
Sex distribution among subjects examined after dilatation of the pupil

	Bergen		Birmingham		Bonn		Combined	
	No examined	Per cent	No examined	Per cent	No examined	Per cent	No examined	Per cent
Men	210	27 4	298	37 2	91	18 5	599	29 1
Women	556	72 6	503	62 8	400	81 5	1459	70 9
Total	766	100 0	801	100 0	491	100 0	2058	100 0

fore and after dilating the pupils with homatropin These persons comprised about 80 % of the total number living in these old people s homes

In England the investigation was carried out in Birmingham in 1966 in the *geriatric departments of 4 different hospitals* and in 2 old people s homes This material comprised 801 persons over 60 years all examined under Cyclogyl (Schieffelin) mydriasis From the old people s homes the attendence was about 30 % whilst practically all the ambulant patients in the geriatric departments were examined

In Germany, the investigation was carried out in 1967 at 17 different homes for the aged in and around Bonn This material consists of 491 persons over 60

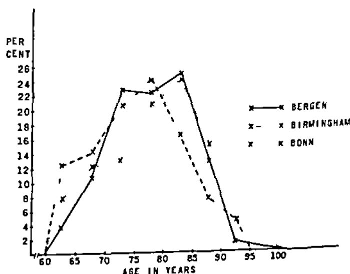


Fig 1
The age distribution in 5 year age groups of men

Table 7

Distribution of unilateral and bilateral fibrillopathy

Fibrillopathy	Bergen		Birmingham		Bonn		Combined		Total	Per cent
	Men	Women	Men	Women	Men	Women*	Men	Women		
Unilateral	2	27	2	3	3	5	7	35	42	41 2
Bilateral	5	14	6	21	4	10	15	45	60	58 8
Total	7	41	8	24	7	15	22	80	102	100 0

1 woman with unilateral anophthalmus excluded

The combined material from all three places comprises 2058 persons of whom 103 had fibrillopathy i e 5 0 %

The distribution of unilateral and bilateral fibrillopathy in the three materials is shown in table 7

Where fibrillopathy was demonstrated the condition was unilateral in 41 2 % and bilateral in 58 8 % of the cases

Comments

The investigations in Bergen Birmingham and Bonn were carried out under conditions of such similarity that the results should be comparable

The age distribution in the materials is so close for both men and women that direct comparisons have been made For men the observed differences in incidence of fibrillopathy in Bergen Birmingham and Bonn are not statistically significant (P = 0 10) For women the difference in the incidence is on the border of statistical significance (P = 0 05)

The differences in the incidence of fibrillopathy observed between men and women both in the individual places and combined are not statistically significant (Bergen P – 0 05 0 10 Birmingham P = 0 10 0 20 Bonn P = 0 10 0 20 Total P = 0 05 0 10)

If the materials from Bergen Birmingham and Bonn *are regarded as representative* for the age groups examined in the respective countries *the main impression is that fibrillopathy is far more frequent in England and Germany than was previously thought and that the frequency is not essentially different from that seen in Norway*

Thus the results of the present investigations discredit the general view that there is considerable variation in the geographical distribution of fibrillopathy

Table 4

Incidence of fibrillopathy in men

Age	Bergen			Birmingham			Bonn			Combined		
	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent
60 69	30	1	3.3	79	0	0	18	1	5.5	127	2	1.6
70 79	95	3	3.2	134	3	2.2	31	1	3.2	260	7	2.7
80 89	81	3	3.7	72	4	5.6	36	3	8.2	189	10	5.3
90 99	4	0	0	13	1	7.7	6	2	33.3	23	3	13.0
Total	210	7	3.3	298	8	2.7	91	7	7.7	599	22	3.7

Table 5

Incidence of fibrillopathy in women.

Age	Bergen			Birmingham			Bonn			Combined		
	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent
60 69	87	3	3.4	63	4	6.4	41	1	2.4	191	8	4.2
70 79	251	17	6.8	164	3	1.8	166	2	1.2	581	22	3.8
80 89	201	20	10.0	244	13	5.3	170	10	5.9	615	43	7.0
90 99	17	1	5.9	32	4	12.5	23	3	13.0	72	8	11.1
Total	556	41	7.4	503	24	4.8	400	16	4.0	1459	81	5.6

Table 6

Incidence of fibrillopathy in men and women

Age	Bergen			Birmingham			Bonn			Combined		
	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent	No investigated	With fibrillopathy No	With fibrillopathy Per cent
60 69	117	4	3.4	142	4	2.8	59	2	3.4	318	10	3.1
70 79	346	20	5.8	298	[illegible]	2.0	197	3	1.5	841	29	3.5
80 89	292	23	8.2	316	17	[illegible]	206	13	[illegible]	804	[illegible]	[illegible]
90 99	21	1	4.8	45	5	11.1	29	[illegible]	17.2	95	11	11.[illegible]
Total	[illegible]	48	[illegible]	801	[illegible]	4.0	491	23	4.7	[illegible]	103	[illegible]

have found a considerably higher frequency of glaucoma than would be expected in an average population – 17 6 % (*Trantas* 1934) 9 7 % (*Baumgart* 1933) and 9 5 % (*Joannides & al* 1961) Even if the fibrillopathy frequency is calculated after excluding glaucoma patients such materials cannot automatically be taken as representative of the general population

The significance of sex distribution is uncertain Some authors have found higher frequencies in women than in men (*Hørven E* 1935 *Bitran & Villalobos* 1959 *Lowe* 1964 *Backhaus & Lorentzen* 1966 *Klouman* 1967) others the contrary (*Busacca* 1928 *Orgen* 1949 *Joannides & al* 1961 *Gillies* 1962 *Clements* 1968) and one has found almost equal incidence (*Rehsteiner* 1929)

None of the differences in the present material was statistically significant

Sex distribution thus seems to be of less importance but should be analysed in studies of fibrillopathy distribution

Interest of the examiner in the condition is as important as accuracy Several authors have maintained this (*Sobhy Bey* 1932 *Maghraby* 1937 *Garrow* 1938 *Bedell* 1940 *Irvine* 1940 *Berliner* 1951 *Ashton* 1957 *Audibert* 1957 *Gifford* 1957 *Tarkkanen* 1962) Inexperienced investigators readily overlook the condition and its demonstration is often dependent on its being specially sought Little interest in fibrillopathy may be the reason for the condition being previously regarded as rare in Denmark (*Ehlers* 1936 *Holm Pedersen* 1952 and 1954) Similarly it has been generally regarded as a rare condition in Sweden More recent systematic investigations however have shown that the incidence of fibrillopathy in Denmark and Sweden hardly differs from that in Norway (*Stromberg* 1962 *Ladekarl* 1965 *Backhaus & Lorentzen* 1966) The relatively low incidence in one of the materials from U S A (*Lemoine* 1950) may have the same cause This material was collected by reviewing case notes from an eye clinic The author had not himself examined all the patients and thus the accuracy and interest of chance examiners had a considerable influence on the results More recent work from U S A (*Hørven I* 1966) shows conditions more in agreement with Norwegian investigations (*Aasved* 1969 a)

It is a common view that fibrillopathy occurs very frequently in Norway This view is to a great extent based on 5 glaucoma materials with incidence ranging from 77 % to 93 % (*Hørven E* 1935 1936 1937 *Holst* 1947 *Thomassen* 1949 *Petersen* 1958)

However it is doubtful whether these studies give a correct picture of Norwegian glaucoma patients in general Several factors may have contributed to these high figures

The 5 investigations came from the same eye clinic where the ophthalmologists were specially interested in fibrillopathy They are from a period prior to the performance of routine tonometry on eye patients above a certain age The glaucoma cases admittet to the hospital may have been suffering from

The results when compared with those of other investigations emphasize the importance of taking a number of factors into consideration when comparing the incidence of fibrillopathy in various population groups Some of these factors will be mentioned here in addition to comments on some of the earlier investigations which have formed a basis for the assumption of considerable geographical variation in distribution

Age distribution of those examined has great significance In a population study of 8537 persons with presumably healthy eyes in Bergen an increase in the incidence of fibrillopathy from 0 4 % in the age group 50 59 years to 7 9 % in the group 80 89 years was found (*Aasved* 1969 b)

The youngest person with fibrillopathy described in the literature up to now was 31 years old (*Horven & Hutchinson* 1967) The average age for subjects with fibrillopathy in various previous works is from 65 to 78 years (*Maghraby* 1937 *Wilson* 1953 *Gifford* 1957 *Tarkkanen* 1962 *Jones* 1962 *Gillies* 1962 *Lowe* 1964 *Ladekarl* 1965 *Aasved* 1969 b)

The frequency of fibrillopathy also increases with age among patients with open angle glaucoma (*Aasved* 1969 a) In previous publications the age groups are variable This makes direct comparison of the materials impossible

Selection for examination is very important It is well known that persons with fibrillopathy often also have glaucoma Thus there will be a marked difference in the frequency of fibrillopathy in the materials of glaucoma patients only and materials without glaucoma patients The close correlation between fibrillopathy and glaucoma applies to open angle glaucoma whilst patients with narrow angle glaucoma show scarcely any increase in frequency of fibrillopathy over the population in general (*Baumgart* 1933 *Gradle & Sugar* 1940 and 1947 *Holst* 1947 *Horven E* 1948 *Ross* 1949 *Gillies* 1962 *Tarkkanen* 1962 *Lowe* 1964) The incidence will therefore depend on whether or not the glaucoma material contains a mixture of the two types of glaucoma

Nor can various reports concerning patients with open angle glaucoma be directly compared Such materials gathered in Bergen in different ways suggest that the frequency of fibrillopathy is higher among the serious cases of glaucoma than among the milder cases (*Aasved* 1969 a) This is also supported by several authors who maintain that glaucoma capsulare is a more serious form than glaucoma simplex (*Vogt* 1930 *Graedielski* 1931 *Blaickner* 1937 *Joannides & al* 1961 *Tarkkanen* 1965 *Horven I* 1966)

In general studies from eye specialist practices outpatient clinics or hospital departments will hardly be representative of the general population Such studies are likely to include over representation for example of patients with glaucoma and fibrillopathy This may apply to some Greek and Italian investigations showing a relatively high incidence of fibrillopathy where the authors

have found a considerably higher frequency of glaucoma than would be ex pected in an average population – 17 6 % (*Trantas* 1934) 9 7 % (*Baumgart* 1933) and 9 5 % (*Joannides & al* 1961) Even if the fibrillopathy frequency is calculated after excluding glaucoma patients such materials cannot automatic ally be taken as representative of the general population

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However it is doubtful whether these studies give a correct picture of Nor wegian glaucoma patients in general Several factors may have contributed to these high figures

The 5 investigations came from the same eye clinic where the ophthalmo logists were specially interested in fibrillopathy They are from a period prior to the performance of routine tonometry on eye patients above a certain age The glaucoma cases admittet to the hospital may have been suffering from

serious glaucoma Thus at least 26 of the 48 glaucoma patients in one of the materials had absolute or almost absolute glaucoma *(Horven E 1935)*

Nor has this clinic a natural geographic area from which it receives all glaucoma patients Ophthalmologists over a wider area may perhaps send their serious glaucoma cases to this hospital while they themselves manage the more easily controlled cases It is also possible that because of great interest fibrillopathy has been demonstrated first by the slit lamp and then as a result of this the patient has been examined for glaucoma

The 5 reports may thus have comprised specially selected glaucoma patients who gave over representation of glaucoma capsulare They do not therefore give a uniform picture of fibrillopathy incidence among Norwegian glaucoma patients

Satisfactory conditions for detecting the disease are of importance A slit *lamp examination in a dark room is necessary The light must fall obliquely* on the lens surface Many cases cannot be discovered in eyes with small pupils In 5 of the 48 cases in the Bergen material the changes could not be seen until the pupils were dilated This was among persons over 60 years of age where the changes would be expected more pronounced than in younger persons That the pupils often dilate badly in eyes with fibrillopathy is also a difficulty Unfavorable conditions for examination may have contributed to the low incidence in one investigation in London *(Thomassen 1949 1966)* In addition this material comprised a rather small number of patients (50 eyes)

The size of the material has significance in investigations on a condition with a low incidence *in the general population Many studies in tabl* I must be regarded as too small to form a basis for comparing the incidence of fibrillopathy

The glaucoma material from the Isle of Man was not sufficiently large for the division into native and non native groups which gave the impression that the incidence of fibrillopathy was much higher among those born on the island than among newcomers The high frequency in the first group was thought to be due to the Scandinavian ancestry of the population *(Clements 1968)*

Familial occurrence of fibrillopathy has been described by several authors *(Vogt* 1930 *Gifford* 1957 *Amalric & al* 1960 *Tarkkanen* 1962 and 1965 *Bertelsen* 1966 *Sæbo* 1967 *Klouman* 1967) In the present material from Bonn fibrillopathy was observed in two sisters These examples may indicate a hereditary factor in fibrillopathy and this might be of some significance for the incidence of the condition in local population groups The high frequency of fibrillopathy on one of the Åland Isles *(Forsius & Eriksson* 1961) may possibly be explained on this basis

Conclusion

The abundant material concerning the incidence of fibrillopathia epitheliocapsularis suggests that this condition is not associated with any particular race nor does it appear with special frequency under particular climatic conditions In addition to the investigations included in the tabular surveys it may be mentioned that fibrillopathy has been demonstrated in Arabs (*Arguello & Tosi* 1938) negroes in America (*Gradle & Sugar* 1947 *Hørven I* 1966) in persons from North Africa (*Audibert* 1957) from Uganda (*Davanger* 1968) and in Lapps (*Ihler* 1964) No relationship to nutritional conditions has been shown

Thus fibrillopathy seems to occur all over the world

The demonstration of fibrillopathy in several persons of the same family suggests that heredity may influence the incidence in local population groups

This investigation shows that fibrillopathy occurs far more often in England and Germany than was thought after earlier studies and that the frequency in these countries is scarcely different from that in Norway

The great differences shown by earlier investigations are thought to be due to inequalities in the age distribution composition and size of the material and in the interest and accuracy of the investigators as well as to variations in the conditions of the examination

The theory of considerable variation in the geographical distribution of fibrillopathy does not therefore seem to be valid

Summary

The incidence of fibrillopathia epitheliocapsularis so called senile exfoliation or pseudoexfoliation of the anterior lens capsule has been investigated among persons over 60 years of age in Bergen Birmingham and Bonn The frequency found among men was 3 3 % 2 7 % and 7 7 % respectively These differences are not statistically significant Among women the incidence was 7 4 % 4 8 % and 4 0 % respectively The differences here are on the border of statistical significance

The great differences in fibrillopathy frequency shown in some earlier investigations may be due to variations in the age distribution composition and size of the material in the interest and accuracy of the examiners and in the condition of examination of the patients Several reports on familial incidence may indicate that heredity influences the frequency in local population groups

The common view of considerable variations in the geographical distribution of fibrillopathy does not seem to be valid

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From the University Eye Clinic
(Head Professor Holger Ehlers M D) Rigshospitalet Blegdamsvej Copenhagen

LEBER s DISEASE IV

BY

TOVE SEEDORFF

Summary

This paper is the 4th of a series which aims at completing previously reported families with optic neuritis and thereby at contributing a share in the discussion on its mode of inheritance The family in question comprises 44 persons distributed over 6 generations It is characterized by a high rate of manifestation among males as well as females by a high infant mortality and by case histories of extremely varied course The discussion concerns the pathognomy of the disease and the differential diagnosis from infantile optic atrophy

Material and Methods

The family was first described in 1944 by *Lundsgard* who called it family G *Godtfredsen* (1949) added one case occurring in 1948 The lines for reconstructing and supplementing the material have been described in previous papers (*Seedorff* 1968) Six new cases have been found 5 of which were reported by the women of the family while the 6th case *was traced* by sending an inquiry about all members of this family to those eye departments where they might be expected to be admitted if they had an eye disea e

Position of Previous Authors Patients in the Pedigree
Jensen s No 67 who was *Lundsgard s* Case 63 is G 2 in the present pedigree
Lundsgård s Case 64 is G 7 Case 65 is G 8 Case 66 is G 18 Case 67 is G 32
Godtfredsen s case is G 22

Received May 31st 1968

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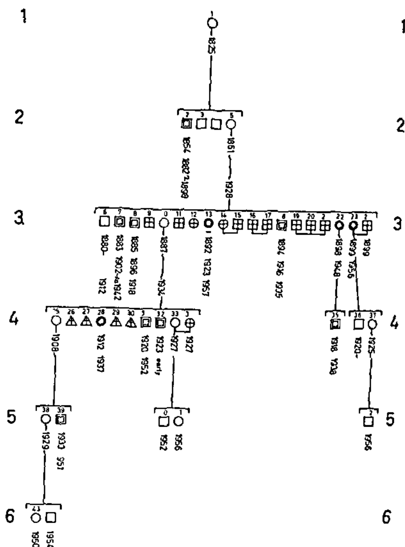


Fig 1
Pedigree G

Corrections to the 1944 Pedigree

Within the sibship G 25 34 the present study revealed 5 children living to be older than 10 years while *Lundsgard* had found 3 The eldest child was born in 1908 while *Lundsgard* stated 1920

Additions to the 1944 Pedigree

Godtfredsen s case G 22 has been inserted In addition another 6 cases have been demonstrated and two carriers have been disclosed The patients are G 13 G 23 G 28 G 31 G 32 and G 39 the carriers are G 10 and G 25 Among the manifestations 3 occurred prior to 1944 and 3 later

Size of Pedigree
44 persons 16 females 24 males 4 of unknown sex An infant mortality of 36 % (approx 16 out of 44) however reduces the material only 28 persons – 13 females and 15 males – having attained an age at which manifestation may be expected

Number of Manifestations Among Males
A calculation may be made for the 3rd generation which comprises only one sibship A member of this sibship has reported that her mother bore 21 children but she was unable to give any data concerning the deceased siblings *Lundsgard* looked for 20 children and succeeded in recording 19 Four out of the 13 recorded boys lived to be older than 10 years 3 of the 4 – perhaps all (cf case histories) developed the disease The time of onset of optic neuritis in the 3 proven cases ranged from 11 to 22 years of age

The numbers involved are so small that it is unsatisfactory to calculate per centages Only it strikes one that the age at manifestation is early and the rate of manifestation very high

Number of Carriers and of Manifestations Among Females
A calculation is permissible for the 3rd generation just as for the males 4 of the recorded 6 girls lived to be 10 3 of the 4 girls developed the disease and *the 4th* one was a carrier The age at onset ranged from 31 to 57 years It is *striking* that the time of manifestation in two cases is late and that the rate of manifestation is very high

Non carriers
It is not possible to prove for any woman of the *pedigree* that she is not a carrier

Causes of Death
The high infant mortality in the 3rd generation may be explained by the fact that the deceased infants were twins or triplets and that the family lived under poor circumstances in Copenhagen before the turn of the century

The causes of death in the sibship G 25 34 are unelucidated

There were two cases of sudden death at an early age among the males of the 3rd generation G 6 died suddenly at his workplace at the age of 32 His fellow workers found him *sitting dead* G 8 also died suddenly He was taken ill in a tram was helped to get home carried upstairs and died an hour later aged 33 years The causes of death are unknown

In two cases G 13 and G 18 tertiary syphilis was among the causes of death

Reliability of the Pedigree and Recording of the Cases

The 1st and 2nd generations have to be rejected as a basis for calculation as it cannot be ruled out that the sibship of the 2nd generation was larger than stated and as there is no information about vision in G 1 G 3 and G 4 Apart from the slight uncertainty concerning the number of deceased children in the 3rd generation I consider this generation and the subsequent ones to have been reliably recorded

Case Histories

6 cases are typical with a well described stage of optic neuritis G 7 G 8 *(Lundsgard s* probands) G 22 G 31 G 35 and G 39 4 cases are atypical or incompletely described G 2 G 13 G 28 and G 32 1 case is atypical because of severe peripapillary changes G 23 2 cases are complicated by syphilis G 13 and G 18 *(Lundsgard s* proband)

G 1 No data concerning vision or age at death

G 2 N P H born 1854 *Edmund Jensen s* No 61 *Lundsgård s* Case 63 *Grut s* protocol 1882 F III 1200

1882 28 year old labourer His eyesight had always been very poor However he had been able to shoot quite well as a conscript During the past year considerable deterioration of the eyesight Visual acuity in each eye Finger counting at 4 6 feet Central scotoma in both eyes Able to discern all colours by eccentric fixation if only the objects are fairly large No appreciable narrowing of the visual field Ophthalmoscopy Blurred limits of the discs Vessels greatly tortuous and congested *Comments* If the impairment of vision set in one year prior to the examination optic atrophy would have been expected to be present at the time of the examination If the impairment is assumed to have been due to the sequelae to optic neuritis during childhood optic atrophy would also have been expected to be present at the time of examination Attention must be applied on this discordance between the history and the interpretation of the ophthalmoscopic finding

G 3 No data concerning vision or duration of life

G 4 No data concerning vision or duration of life

G 5 According to her daughters she had a good eyesight until she died at 6[illegible]

G 6 A H born 1880 died in 1912 at the age of 32 According to *Grut s* protocol 1902 K VI 982 his brother G 7 stated in 1902 that G 6 and G 8 were suffering from the same affliction as himself *Lundsgård* recorded G 6 as unaffected in 1944 although she had read these notes stating some of his sibs still living say that he had good sight His sister G 27 who was 14 when he died stated in 1960 that his eyes had been rather bad but she could not imagine that he had had Leber s disease because he could always manage his work as foundry worker *Comments* The notes from 190[illegible] are probably more reliable than the information given by his sister and children who were very young when he died

G 7 E M W H born 1883 *Lundsgard s* Case 64 *Grut s* protocol 1902 K VI 98 1902 A 19 year old labourer with a history of visual impairment for 6 months Ophthalmoscopy Signs of optic neuritis in both eyes Visual acuity 5 36 in both eyes Visual field A scotoma difficult to demonstrate below the point of fixation Peripheral

restriction of the visual field Two months later Bilateral atrophy of the discs 190? 1908 Decreasing visual acuity 1936 Visual acuity in right eye 1/60 in left eye 3/60 A central scotoma could not be demonstrated but eccentric fixation was observed

G 8 I H H born 1885 *Lundsgård's* Case 65 *Grut's* protocol 1896 H V 679 1896 11 year old son of a labourer His vision had been deteriorating for 2 months Ophthalmoscopy Signs of optic neuritis in both eyes Visual acuity less than 5/60 in both eyes Six weeks later Bilateral atrophy of the discs 1902 Better vision almost 5 1? in both eyes A central scotoma could not be demonstrated Outer limits of the field good for hand 1914 Visual acuity in both eyes about 5/36

G 10 J K C G born 31 12 1887 died in 1934 at the age of 47 Her oldest daughter reported in 1960 that G 10 had good eyesight

G 13 B C J born 28 1 1892 Frederiksberg Hospital Med Dept B No 1399/57 This patient died after *Lundsgard's* study was completed but before the present study was instituted *Lundsgard* recorded her as unaffected When her sisters in 1960 reported that her eyesight had been so poor that she could hardly read even with a hand lens information was sought at Frederiksberg Hospital where she had been admitted 7 times during the period 1950 1957 and had died in 1957 aged 65 At ophthalmological examination in 1955 the patient stated that she had noticed visual impairment in 1923 that most male members of her family had the disease but only a few of the women She felt that her vision had probably deteriorated a good deal since 1923 and that, in particular the visual field had become greatly restricted Ophthalmoscopy Severe atrophy of both discs which were yellowish pale *In addition hypertensive* and arterio sclerotic angiopathy Fundus hypertonicus II Visual acuity *in right eye* 6/60 in the left eye 6/24 Pupils rather inactive to light Visual fields *Concentric narrowing to* 1 Conclusion Presumably Leber's optic atrophy hardly of syphilitic *origin* Other diagnoses in 1957 Heart disease (perpetual arrhythmia myocardial degeneration) arterial hypertension history of syphilis (1923) aortic ectasia (syphilitic) *emboli in* popliteal arteries *Comments Primary syphilis set in 1923* the same year as the visual impairment Since luetic diseases of the optic nerve *occur* in a later stage it is unlikely that the syphilis could have been the cause of the visual impairment in 1923 Unfortunately there are no ophthalmoscopic data from 1923 The disease has been characterized by restriction of the visual field and steady *deterioration* This is not characteristic of Leber's disease but it does occur in rare cases It *seems* useless to discuss which disease made this patient blind It is simpler to establish that there were competitive causes of her visual nerve atrophy

G 18 H C B H born 17 10 1894 Lundsgård's case 66 University Out patient Eye Clinic 963 1917 University Psychiatr Dept 676 1935 Visual impairment started in the left eye in 1916 and appeared 6 months later in the right eye Ophthalmoscopy 3 months after the onset in the *right* and 9 months *after* the onset in the left eye Signs of optic neuritis in the right eye atrophy of the left disc Visual acuity in right eye 6/36 in left eye 3 60 Visual field on the right The patient did not exhibit a central scotoma but the ophthalmologist observed eccentric fixation normal periphery Visual field on the left *Central* scotoma combined with a nasal defect. 1918 1935 4 ophthalmological examinations showed deteriorating vision The patient died in 1935 aged 41 of bronchopneumonia Other diagnoses *Syphilitic* encephalopathy mental confusion with hallucinations emaciation *During the last years the* visual acuity in the right eye deteriorated to finger counting before the eye *in the left* eye only perception of light The right pupil reacted to light while the left one did *not* In addition tremor of the *arms* tongue and jaw and indistinct speech W R positive in the blood as well

as spinal fluid *Comments* optic neuritis was observed in 1917 while the time of the syphilitic complication is unknown Therefore Leber s disease was the most likely diagnosis in 1917 Just like G 13 this case is characterized by peripheral narrowing of the visual field and deteriorating vision perhaps because of competitive causes of the optic nerve lesion

G 22 K H P A *born 31 5 1898 Godtfredsen 1949 Copenhagen City Hospital Eye* Department 498/1948

14years prior to the visual impairment she had been admitted to Frederiksberg Hospital *for lipothymia* X *rays of the skull* Enlarged sella turcica

1948 A 50 year old matron Ophthalmoscopy 3 months after the vision had started deteriorating Signs of optic neuritis in both eyes Visual acuity in both eyes 1/60 Visual field Normal outer limits central scotoma of 10° for white 10/300 X rays of skull Enlarged sella turcica Air encephalography Cerebral atrophy of the ventricular type 1950 Ophthalmoscopy Sharp edged atrophic greyish white discs Vision and visual field unchanged

G 23 E S born 28 10 1899 University Out patient Eye Clinic 1955 and 1960
1955 A 57 year old widow controller of photographic paper Ophthalmoscopy two weeks after visual impairment had been noted in the left eye Right eyeground normal Around the left disc a stellate figure not exudative Visual acuity in right eye 6 9 in *left eye 2/10* 6 weeks later Ophthalmoscopy *Both discs now of same appearance as* described for the left one in the previous examination Neurological examination was not done and blood samples were not obtained as the patient stopped attending 1960 The patient was sent for Ophthalmoscopy Porcelain white atrophic discs and in the surroundings severe degenerative changes Visual acuity in right eye 0 5/60 in left eye 1/60 with eccentric fixation The central scotoma was very large As the patient was unable to fixate steadily the investigation of the visual field on a screen was illusory Optically elicited eye movements could be aroused from any section of the periphery of the visual field resulting in a coarse nearly rotatory nystagmus W R in the blood negative The patient refused to have further examinations *Comments* The ophthalmoscopic finding is atypical owing to the severe permanent changes in the surroundings of the disc The central scotoma was larger than usual No neurological or radiological examinations have been performed

G 25 K M V C born 14 10 1908 Good vision when examined in her home in 19[illegible]
Impaired hearing since childhood

G 28 O C J G born 15 9 1912 University Out patient Eye Clinic 1937 and 19[illegible]
1937 A 25 year old factory girl Ophthalmoscopy 3 weeks after visual impairment had been noticed in the right eye Normal Visual acuity in right eye 1/36 in the left 6 4 5 Nothing noted concerning the visual field

1962 The patient was sent for She said that in 1937 for fear of an operation she had stopped attending ophthalmological examination although for a time her vision was so poor that she had difficulty in moving about in the streets and could neither read *nor sew* The vision then improved and at the end of one year she could again see clearly Since then she had been suffering from flickering before the eyes especially the right followed by headache Ophthalmoscopy Temporal atrophy of the right disc *no visible atrophy* on the left Visual acuity in right eye 6/18 in the left 6 4 5 Visual field Central scotoma for a red object 5/1000 on the right paracentral scotoma for a red object 5/1000 on the left *Comments* There was no visible sign of optic neuritis at *the time of the fundus* examination The history indicates that the disease became bilateral in the course of 1937 Later it assumed an asymmetrical course the scotoma in

the left eye becoming paracentral as found in 1960 The visual acuity in the left eye became extremely high and is paradoxical but in principle a paracentral scotoma is an acceptable though rare type of Leber s disease

G 31 I W G born 1.3 1920 Copenhagen City Hospital Eye Department 800/1952 1952 A 32 year old labourer Typical case of Leber s disease with a well defined initial stage and regular course

G 3 P E G born 15 2 1923 Copenhagen City Hospital Eye Department 2331/1945 1945 A 22 year old labourer who reported that his eyesight had always been poor Ophthalmoscopy Temporal pallor of the disc in both eyes vessels rather tortuous Visual acuity in right eye Less than 6/24 + 2 5 sph Visual acuity in left eye 6/24 + 3 0 sph Visual field in both eyes Normal outer limits for white considerable con centric narrowing for red

In 1965 the patient was examined in his home He stated that he had always had a poor eyesight and had never noticed that it had deteriorated He did not remember whether he had been examined by an ophthalmologist as a child He had attended normal school and had learnt to read without spectacles but he had never read much He had been assistant in a milk truck and was now working in a dairy where his duties were to collect bottles into crates and place them on a conveyor belt. Ophthal moscopy Bilateral atrophy of the discs Visual acuity in right eye 4/18 without cor rection in left eye 4/36 without correction The patient did not use eccentric fixation. Visual field Normal outer limits to hand central scotoma not demonstrable perhaps because of the conditions under which the examination was carried out A test with American Optical Company s colour tables showed the patient to be moderately red green blind *Comments* Optic neuritis had not been observed in this case perhaps be cause the initial stage remained undetected during early childhood The visual acuity is relatively good and possibly explains why the patient does not make use of eccentric fixation A central scotoma for red would presumably be demonstrable under better conditions for examination

G 33 A I H born 1 7 1927 Not examined

G 34 (twin of G 33) Died at 10 months of pneumonia

G 35 T B H A born 14 7 1918 Lundsgård s case 67 Frederiksberg Hospital Eye Department 1938 Typical case of Leber s disease which set in at the age of 20

G 36 E S born 23 2 19 0 Examined in his home in 1965 Good vision

C 37 T R R born 22 5 1925 Good vision in 1965 according to her brother and hus band

G 38 K B P born 15 1 1929 Good vision in 1965 according to her mother

G 39 P V C born 24 11 1933 Copenhagen City Hospital Eye Department 635/1951 Typical case of Lebers disease which set in at the age of 18

G 40 H R born 23 1956 According to private ophthalmologists information in 1965 Myopic astigmatism No other abnormalities

The remaining 5 persons of the ped gree have not been examined

Discussion

The result of this study was like that of my previous studies *(Seedorff 1968)* non carriers could not be demonstrated

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G 28 O C J G born 15 9 1912 University Out patient Eye Clinic 1937 and 1962

1937 A 25 year old factory girl Ophthalmoscopy 3 weeks after visual impairment had been noticed in the right eye Normal Visual acuity in right eye 1/36 in the left 6/4 5 Nothing noted concerning the visual field

1962 The patient was sent for She said that in 1937 for fear of an operation she had stopped attending ophthalmological examination although for a time her vision was so poor that she had difficulty in moving about in the streets and could neither read nor sew The vision then improved and at the end of one year she could again see clearly Since then she had been suffering from flickering before the eyes especially the right followed by headache Ophthalmoscopy Temporal atrophy of the right disc no visible atrophy on the left Visual acuity in right eye 6/18 in the left 6/4 5 Visual field Central scotoma for a red object 5/1000 on the right paracentral scotoma for a red object 5/1000 on the left *Comments* There was no visible sign of optic neuritis at the time of the fundus examination The history indicates that the disease became bilateral in the course of 1937 Later it assumed an asymmetrical course the scotoma in

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In this pedigree the discussion on manifestations during childhood does *not* influence that on the number of carriers because G 5 and *subsequent* carriers all have one or more descendants who have exhibited a typical case of Lebers disease The reason why the author is reserved in drawing a conclusion from this pedigree is that only four women are included in that part of the pedigree which is now ready for calculations

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The pedigree is so small that it belongs to the category in which a high rate of manifestation may be interpreted as an unfortunate accidental unequal distribution of the trait among the members of a few sibships the majority of the viable children having received the trait Accidental accumulation of the trait in sibship C 6 24 in which 7 perhaps all 8 viable children proved to have the trait is not very probable but in sibship G 25 34 in which the trait is present in 4 out of 5 viable children the possibility of accidental accumulation cannot be neglected In respect to carriers the numbers involved are even smaller In sibship G 6 24 there is a question of only 4 women The fact that all four proved to posses the trait may perhaps be due to accidental accumulation In sibship C 25 34 2 out of 3 women have so far proved to possess the trait a small number which cannot form the basis of any conclusion Thus the study accords with the results of studying family A and family C and the high frequency of disease in sibship G 6 24 agress with the assumption that every daughter of a carrier inherits the trait but alone the pedigree appears to be small for giving evidence concerning the carrier rate

One aspect of the case histories demands attention There were 3 reports on impaired vision during childhood One of the patients G 8 demonstrated definite signs of optic neuritis at the age of 11 years but for the other two G 2 and G 32 the age at manifestation is a subject of discussion

The background of the present study was the view that infantile optic atrophy was assumed to differ from Leber s disease in its clinical course as well as in its genetic pattern and it is a presupposition that a distinction between the two diseases can be made by their clinical course alone From Denmark Lundsgård (1944) described 20 families with 101 cases of Leber s disease and Kjer (1959) described 19 families with 249 cases of infantile optic atrophy Both authors concluded that the two diseases differed clearly from each other and it was expected therefore that the present study would reveal exclusively typical cases of Leber s disease The fact that the family included also cases of optic atrophy of obscure origin during childhood does in a way entail an obligation to investigate also the male linage

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lated respectively from the blood spleen or lymphonodes of rabbits sensitized against chicken corneal extracts and for comparison of normal rabbits) in rabbits supporting a long time transparent interlamellar chicken corneal graft

Methods and Materials

Animals Adult male random bred rabbits weighing approximatively 3 kg were used

Px irradiation Total body Rx irradiation (Tele Chobalt Therapy TCT using a Picker therapeutic unit) was given twice at 48 and 24 hours before transplantation in all rabbits The dose was 400 r each time During the irradiation both eyes were sheltered[5] The details of the Rx irradiation technique have been previously described[6]

Sera Two different sera were used

Ist Hyperimmune rabbit anti chicken cornea extract serum (Serum A) This serum was obtained as follows Five male adult random bred rabbits from the same breed as those used in all experiments were actively immunized against chicken corneal extract The chicken corneal extract was prepared in the following way the eyes of about 25 chicken were enucleated and kept in a physiologic solution containing a small amount of antibiotics (Aureomycin 10 m /100 ml saline) The corneas were removed entirely freed of blood and uveal pigment and then carefully washed in saline containing the same amount of antibiotics Corneas were cut into small pieces and homogenized in a Potter apparatus at about 4° C for 15 30 minutes with interruptions to prevent heating The supernatant was centrifuged in the cold (1600 g at 4° C for 15 minutes) and subjected several times to dialysis in cold saline The supernatant was used as antigen to obtain a rabbit anti chicken cornea extract serum It was also used for other purposes as it will be described later The protein content of this extract determined as described by Lowry[7] was of about 10 mg protein/ml This extract was divided into several 1 ml aliquots and kept frozen at -20 C Just prior to use aliquots were defrosted and emulsioned in an equal volume of complete Freund s adjuvant (Difco Detroit Michigan) The first time each rabbit received 5 mg protein of antigen in the footpads and under the skin of the neck (total volume 1 ml) Once every week for a month each rabbit received intradermally a dose of 1 mg of antigen in saline (in a volume of 1 ml each time) Seven days after the last booster (five weeks after the first immunization) rabbits were bled from the central artery of the ear Sera from all 5 rabbits were pooled centrifugated in the cold at 1600 g for 30 minutes and frozen in small aliquotes at -20 C The aliquots were defrosted just be

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EFFECTS OF A PASSIVE ADMINISTRATION OF HUMORAL ANTIBODIES SENSITIZED POLYMORPHOLEUKOCYTES AND IMMUNOLOGICALLY COMPETENT LYMPHOCYTES IN RABBITS SUPPORTING TRANSPARENT INTER-LAMELLAR CHICKEN CORNEAL GRAFTS

BY

FRANCO D ERMO M D MARIO LANZIERI M D
and ROBERTO REVOLTELLA M D *

An interlamellar chicken corneal graft in rabbits becomes generally opaque within a few days after transplantation[1,2] However in rabbits subjected few hours before operation to a total body Rx irradiation this graft usually takes and remains transparent for a long time as long as 6 months to years[3]

There are many evidences to believe that the mechanisms causing a corneal graft clouding are the same as those involved in other tissue graft reactions[4] Although the antigenicity of corneal tissues has been documented in numerous studies involving heterologous and homologous immunization a casual relationship between antibody production and corneal graft rejection still remains to be established

In this paper we describe some earlier biological effects of passive administrations of homologous humoral antibodies of a mixture of macrophages and other polymorpholeukocytes or of selectively purified lymphocytes (cells iso

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Cells suspension Six male random bred rabbits were immunized against chicken cornea extract (the same as above described) in complete Freund s adjuvant They received 5 mg protein of antigen in the four footpads and subcutaneously in the neck only once (total volume 1/ml/rabbit) Four seven and twelve days after immunization the animals were bled by heart puncture Antibody production was investigated in the serum by means of an Ouchterlony test a positive line of precipitation could be detected only after the seventh day from the immunization

Isolation of lymphocytes Lymphocytes were isolated from the blood using the technique described by Sell & C[10] Heparinized blood was filtered through a column of brushed nylon Polymorphs adhered to the fibre but lymphocytes and few red cells passed through the column Beforehand the white cells were isolated from most of the erythrocytes by sedimentation using 5 % dextran (MW 186 000) From the blood of each animal about 2 × 10⁶ lymphoid cells per 1 ml of blood were obtained The viability of the cells tested by trypan blue staining was of about 80 % The immunologic competence of these cells was tested *in vitro* using a modification of the method described by Jerne & Nordin[11] [1] In brief sheep blood erytrocytes suspended in pH 7 2 phoshpate buffer were tanned and coated with chicken cornea extract[11] Washed in buffer cells were suspended 20 % in Eagle s medium and plated 40 × 10⁶ sheep blood erytrocytes coated with chicken cornea extract and 6 × 10⁶ lymphoid cells were suspended in 2 ml of the top layer agar (0 7 % in Eagle s medium) kept melted at + 48° C In order to prevent the anti complementary effect of agar (Special Noble Agar Difco Detroit Michigan) used in the experiment DEAE Dextran (Diethylaminoethyl Dextran) (Pharmacia Uppsala Sweden) 2 mg/ml have been previously added to the agar Immediately afterwards this suspension was plated in a Petri dish of 10 cm width containing a bottom of gelled agar (1 4 % in the same medium) Plates were incubated at 37° C for about 1 hour and then complement was added Freshly obtained guinea pig serum two times absorbed with sheep blood erythrocytes diluted 1 5 in the same medium was used as a source of complement After 1 hour of incubation at 37 C and 2 3 hours at room temperature plates were read The results are summarized in Table 1 Lymphocytes isolated from animals 7 days after immunization gave the greatest number of plaques of hemolysis Lymphocytes from

Table 1

Plaques of hemolysis produced in vitro by single cells (lymphocytes). The cells were isolated from the blood or from the spleen of rabbits immunized against chicken corneal extract in complete Freund's adjuvant. Lymphocytes from normal untreated rabbits were used as controls

Lymphocytes	Days after immunization	Sheep blood erythrocytes passively coated with Chicken corneal extract	Normal Sheep blood erythrocytes	Number of plaques of hemolysis per plate (mean on 3 plates in 2 rabbits)	
				Immunized rabbits	Normal rabbits
Blood lymphocytes (6 × 10 /plate)	4	4×10^7	–	20 (± 6)	8 (± 2)
		–	4×10^7	8 (± [illegible])	6 (± 2)
	7	4×10	–	[illegible]00 (± 35)	10 (± 2)
		–	4×10	10 (± 3)	10 (± [illegible])
	1[illegible]	4×10^7	–	[illegible]0 (± 20)	1[illegible] (± 4)
		–	4×10^7	14 (± 4)	10 (± 3)
Spleen lymphocytes (6×10^6 plate)	4	4×10^7	–	15 (± 3)	10 (± 2)
		–	4×10^7	12 (± 4)	1[illegible] (± 3)
	7	4×10^7	–	400 (± 20)	1[illegible] (± 3)
		–	4×10^7	32 (± 5)	10 (± 4)
	12	4×10^7	–	350 (± 30)	1[illegible] (± 4)
		–	4×10^7	15 (± 5)	10 (± 5)
Lymph nodes and spleen lymphocytes (6 × 10 plate)	4	4×10	–	[illegible]0 (± 3)	10 (± 2)
		–	4×10^7	6 (± 1)	6 (± 1)
	[illegible]	4×10^7	–	350 (± [illegible]0)	1[illegible] (± 4)
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		–	4×10^7	32 (± 5)	10 (± 4)
	12	4×10^7	–	350 (± 30)	12 (± 4)
		–	4×10^7	15 (± 5)	10 (± 5)
Lymphonodes and spleen lymphocytes (6 × 10⁶/plate)	4	4×10^7	–	20 (± 3)	10 (± 2)
		–	4×10^7	6 (± 1)	6 (± 1)
		4×10^7	–	350 (± 20)	12 (± 4)
		–	4×10^7	18 (± 4)	10 (± 3)
	12	4×10^7	–	112 (± 15)	8 (± 4)
		–	4×10^7	7 (± 2)	7 (± 2)

the spleen of the same rabbits were also examined Spleens were dissected and placed in Petri dishes containing a physiologic salt solution and heparin (Liquaemin *100 µg/ml*) and teased with forceps and needles as described by Gesner & Howard[14] The tissue debris was removed by passing the suspension through a thin layer of glass wool Cells were then filtred through a column of brushed nylon The cell suspension obtained at the end contained about 75 80% lymphoid cells and the viability of the cells tested by trypan blue staining was of about 80 85%

In order to be sure to have a final cell suspension with a high rate of immunologically competent cells the technique of production of plaques of hemolysis as described above was performed using a pool of cells isolated from blood and spleen of rabbits *immunized in the same way as described before* bled and then killed 7 days after immunization This pool of cells was used in our experiments Even if it was often shown that concentrated cell suspension sometimes cause fatal emboli when injected intravenously into laboratory animals such mishaps never happened in our experiments using a mixed suspension of spleen and circulating lymphoid cells In any case suspensions stood for *3 4* minutes before being injected to allow large aggregates of cells which are difficult to dissociate to settle out

Macrophages isolation Two rabbits were immunized with chicken cornea extract (1 mg/rabbit) in complete Freund s adjuvant Fifteen days later leukocytes were isolated from inguinal lymphonodes and spleed as described by Gesned & Howard[14] The viability of the cells tested by trypan blue staining was of about 85 *90%* *Their immunological specificity* was *controlled* by the immuno cyto adherence test described by Biozzi & C[15] Briefly 0 1 ml of cells suspension (1 × 10⁷/ml) in Eagle s medium was suspended with 0 1 ml of a 20% suspension in Eagle s medium of sheep erythrocytes tanned and coated with the chicken cornea extract used as antigen (the same described above) in tubes containing 1 ml volume of Eagle s medium *The tubes* were *carefully* shaken at 37° C for 30 minutes and then kept at 90° at 4° C for 16 hours Then the cells of the pellet were carefully resuspended and the presence of typical "rosette" was investigated under mycroscope The results are summarized in Table 2

Technique of transplantation After Rx irradiation (see before) *30 rabbits* were subjected to an inter lamellar chicken corneal transplant using the technique described by *Basu & Ormsby*[16] *Chicken corneas* were removed with a *5* mm keratoplasty trephine and immediately immersed for 2 minutes in an antibiotic solution They were then immersed between the corneal lamellae of the right eye of the rabbits the pockets were closed with a silk sutura *The left* untreated eye was used as control Sixty days after transplant 24 animals that *still showed transparent corneal heterografts* were then divided into groups of 4 animals each The six groups were called Group A B C D E and F

Table 2

Number of rosette produced in vitro by polymorphonucleocytes isolated from the spleen and inguinal lymphonodes of rabbits sensitized 15 days before against chicken cornea extract in complete Freund s adjuvant. Cells obtained from unsensitized animals were used as controls

1×10^4 leukocytes and 1.5×10^7 sheep erythrocytes previously passively tanned and coated with chicken cornea extract were incubated in a final volume 1 2 ml of Eagle s medium slowly rotated for 30 minutes at 37° C and then let to stand for 16 hours at 4° C

Cells	Rosette /1000 nucleated cells (mean in 2 rabbits)
Sensitized polymorphoneucleocytes (from spleen and lymphonodes)	85 0
Unsensitized polymorphonucleocytes (from spleen and lymphonodes)	0 5

Experiments

Group A Each of four rabbits of this group was subjected to an intravenous injection of 6 ml of a hyperimmune rabbit anti chicken corneae extract serum (Serum A)

Group B The four animals of this group received intravenously 6 ml per animal of normal rabbit serum (Serum B)

Group C A suspension of 10×10^6 lymphocytes (spleen and blood lymphocytes) in 6 ml of Eagle s medium were injected intravenously into each of four animals of this group Lymphocytes were isolated from rabbits immunized 7 days before with chicken cornea extract in complete Freund s adjuvant as previously described

Group D Each rabbit of this group received intravenously 10×10^6 lymphoid cells (spleen and blood lymphocytes) from three untreated normal rabbits The serum of these rabbits did not show any band of precipitation when tested in an Ouchterlony with chicken cornea extract

Group E Each rabbit of this group was subjected to an intra peritoneous injection of 10×10^9 polymorphonucleocytes (from spleen and lymphonodes) suspended in 6 ml of Eagle s Medium Leukocytes were isolated from rabbits immunized 15 days before with chicken cornea extract in complete Freund s adjuvant as previously described

Group F 10×10^9 leukocytes (from the spleen and lymphonodes of three untreated normal rabbits) suspended in 6 ml of Eagle s medium were injected intraperitoneously into each rabbits of this group

Immunologic controls Three days before 15 and 60 days after the inter lamellar chicken corneal graft and 7 days after the challenge rabbits of the

six groups in experiments were bled The assay of humoral antibodies against chicken cornea extract was performed using the technique of double diffusion precipitin test as described by Ouchterlony

In order to have more sensitive and quantitative data of the immune response rabbits were bled by heart puncture and immediately afterwards the whole blood was incubated in vitro with chicken cornea extract This technique of essay that we employed is based on the principle that the intereaction of antigen with antibody in whole rabbit blood leads to the release of vasoactive compounds like histamine and serotonin the greatest part of which derives from the platelets and perhaps also from blood leukocytes[1] [0] This technique was recently employed also for investigations of the primary formation of antibodies in rabbits subjected to a heterologous or homologous corneal transplant [1] Even if the role of the vasoactive substances liberating antibodies in the graft rejection process is not yet well clarified this technique appeared to be extremely sensitive for the detection of anti corneal antibodies

About 15 ml of blood were extracted each time from the heart of each rabbit using a 20 ml glass siliconized syringe containing a small amount of heparin (Liquaemin 170 μg/ml) The syringe was carefully shaken and 2 5 ml of heparinized blood was then incubated at 37° C for 60 minutes with 0 6 ml of chicken cornealextract The protein content of our employed antigen was of about 60 μg protein/ml The protein content of antigen was determined before dilution according to Lowry The incubation was performed in labeled 100 × 10 mm serologic glass tubes All glassware was carefully siliconized before A 5 % solution of silicon (Silicone M 441 Imperial Chemical Industries Ltd Stevenstone Aurshire Scotland) in n heptan was used for this purpose After incubation tubes were centrifugated at 4° C for 30 minutes at 800 g Afterwards histamine present in the supernatant was assayed biologically on a guinea pig ileum terminalis preparation in a modified Tyrode bath at 37° C [1] Controls were performed each time and samples of blood of rabbits were incubated with equal amounts of saline instead of antigen A typical protocol of the experiment is described in Table 3

Results

The results are summarized in Tables 4 and 5

Group A Between few hours to one two days after the challenge in all 4 rabbits of this group the corneal graft underwent a typical tissue reaction A white opaque Wessely type ring reaction appeared in the eye supporting the transplant Antibodies against chicken corneal extract were detected in the serum of all these rabbits 7 days after the challenge The presence of antibodies was

Table 3

Experimental protocol for detection an immune response of rabbits bearing a corneal graft, by titration of vasoactive substances liberated from the cells of blood in presence of an Antigen Antibody complex

Tube	Rabbit whole blood	Buffer (ml)	Chicken cornea extract (60 μg protein/ml in buffer) (ml)
1	2 5	0 6	–
2	2 5	–	0 6

shown either in the serum by the Ouchterlony test or by the assay of vasoactive substances liberated from the cells of blood in presence of antigen antibodies complexes Before challenge on the contrary antibodies were never detected in these animals

Group B No reaction was appreciable in the cornea supporting the heterograft in all these animals and antibodies against chicken corneal extract were not detected in these rabbits before or after the challenge

Group C Only one rabbit of this group clouded the interlamellar chicken corneal graft starting from the fourth fifth day from challenge No visible reaction was appreciable before when the transplant appeared perfectly transparent No reaction however was visible in the perifery of the recipient cornea and the Wessely ring reaction was not appreciable Humoral antibodies were not demonstrated in the serum of this animal before or after the challenge In the other animals the graft remained perfectly transparent

Group D No reaction was shown in the cornea supporting the chicken corneal graft which remained transparent even after the challenge Antibodies against the grafts were never detected in these animals

Group E All rabbits of this group clouded the interlamellar heterologous graft between two and five days after challenge Antibodies were detected in the serum of these animals seven days after but not before the challenge

Group F Grafts remained transparent in all these rabbits Antibodies against chicken corneal extract were never detected before or after the challenge

Discussion

Many years ago Wessly demonstrated *in vivo* that an interlamellar cornea injection of antigenic proteins induced a reaction that most of time appeared as

six groups in experiments were bled. The assay of humoral antibodies against chicken cornea extract was performed using the technique of double diffusion precipitin test as described by Ouchterlony.

In order to have more sensitive and quantitative data of the immune response, rabbits were bled by heart puncture and immediately afterwards the whole blood was incubated in vitro with chicken cornea extract. This technique of essay that we employed is based on the principle that the intereaction of antigen with antibody in whole rabbit blood leads to the release of vasoactive compounds like histamine and serotonin, the greatest part of which derives from the platelets and perhaps also from blood leukocytes[17 0]. This technique was recently employed also for investigations of the primary formation of antibodies in rabbits subjected to a heterologous or homologous corneal transplant [1]. Even if the role of the vasoactive substances liberating antibodies in the graft rejection process is not yet well clarified, this technique appeared to be extremely sensitive for the detection of anti corneal antibodies.

About 15 ml of blood were extracted each time from the heart of each rabbit using a 20 ml glass siliconized syringe containing a small amount of heparin (Liquaemin 170 μg/ml). The syringe was carefully shaken and 2.5 ml of heparinized blood was then incubated at 37° C for 60 minutes with 0.6 ml of chicken cornealextract. The protein content of our employed antigen was of about 60 μg protein/ml. The protein content of antigen was determined before dilution according to Lowry. The incubation was performed in labeled 100 × 10 mm serologic glass tubes. All glassware was carefully siliconized before. A 5% solution of silicon (Silicone M 441, Imperial Chemical Industries Ltd, Stevenstone, Aurshire, Scotland) in n-heptan was used for this purpose. After incubation tubes were centrifugated at 4° C for 30 minutes at 800 g. Afterwards histamine present in the supernatant was assayed biologically on a guinea pig ileum terminalis preparation in a modified Tyrode bath at 37° C [1]. Controls were performed each time and samples of blood of rabbits were incubated with equal amounts of saline instead of antigen. A typical protocol of the experiment is described in Table 3.

Results

The results are summarized in Tables 4 and 5.

Group A. Between few hours to one two days after the challenge in all 4 rabbits of this group the corneal graft underwent a typical tissue reaction. A white opaque Wessely type ring reaction appeared in the eye supporting the transplant. Antibodies against chicken corneal extract were detected in the serum of all these rabbits 7 days after the challenge. The presence of antibodies was

Table 5

Effects of the chellenges in rabbits in experiments

Animals	Challenge	Route of administration	Craft opacification	Interval of time from the chellenge to the graft opacification	Immune response (detection of antibodies 7 days after the chellenge)
Group A	Hyperimmune ral bit Serum	intra venously	4/4	few hours 2 days	positive (in all rabbits)
Group B	N rmal rabbit Serum	intra venously	0/4	–	negative
Group C	Immunologically competent rabbit lymphocytes	intra venously	1/4	2 6 days	negative
Group D	Un sensitized ral bit lymphocytes	intra venously	0/4	–	negative
Group E	Sensitized rabbit macrophages and other leukocytes	intra peritoneously	4/4	2 6 days	positive (in all rabbits)
Group F	Un sensitized rabbit macrophages and other leukocytes	intra peritoneously	0/4	–	negative

Table 4

Histamine specifically releases per 2 5 ml of blood in rabbits in experiments 0 6 ml of chicken corneal extract (60 μg protein/ml) were incubated in 2 5 ml of rabbits whole blood at 37° C for 1 hour Tubes were then centrifugated at + 4° C at 800 g for 30 minutes Histamine present in the supernatant was assayed biologically on a quinea pig ileum terminalis preparation The values have been calculated by direct interpolation of the response obtained with each sample of the histamine calibration curve for the indicator ileum strip The values obtained for spontaneous release were substracted from values obtained for specific release

Animals		μg Histamine specifically released per 2 5 ml of blood			
		3 days before transplant	15 days after transplant	60 days after transplant	7 days after challenge
	1	0 14	0 22	0 26	1 10
Rabbits of	2	0 18	0 22	0 24	0 90
GROUP A	3	0 20	0 20	0 22	1 25
	4	0 22	*0 21*	0 22	1 28
	1	0 20	0 24	0 28	0 55
Rabbits of	2	0 18	0 28	0 24	0 20
GROUP B	3	0 14	0 22	0 28	0 18
	4	0 16	0 25	0 20	0 16
	1	0 12	0 16	0 21	0 20
Rabbits of	2	0 10	0 18	0 20	0 24
GROUP C	3	0 12	0 20	0 20	0 22
	4	0 25	0 22	0 24	0 26
	1	0 20	0 15	0 20	0 22
Rabbits of	2	0 22	0 18	0 21	0 25
GROUP D	3	0 24	0 18	0 15	0 25
	4	0 24	0 26	0 22	0 30
	1				
Rabbits of	2	0 12	0 22	0 22	1 10
GROUP E	3	0 22	0 28	0 25	0 90
	4	0 12	0 20	0 26	1 15
	1	0 20	0 20	0 20	0 30
Rabbits of	2	0 20	0 26	0 22	0 30
GROUP Γ	3	0 30	0 26	0 30	0 26
	4	0 20	0 20	0 15	0 24

a white gray halox surrounding the spot of the injection [3] It was shown that this halo was formed by antigen antibodies precipitates and by an extremely dense and localized accumulate of lymphoid cells mainly lymphocytes and

Table 5

Effects of the chellenges in rabb ts in experiments

Animals	Challenge	Route of administration	Graft opacification	Interval of time from the chellenge to the graft opacification	Immune response (detection of antil odies 7 days after the chellenge)
Croup A	Hyperimmune ral bit Serum	intra venously	4/4	few hours 2 days	positive (in all rabbits)
Gr up B	Normal ral bit Serum	intra venously	0/4	-	negative
Croup C	Immunologically competent rabbit lymphocytes	intra venously	1/4	2 6 days	negative
Croup D	Un sensitize l rabbit lymphocytes	*intra* venously	0/4	-	negative
Group E	Sensitize l rabbit macrophages and other leukocytes	intra peritoneously	4/4	2 6 days	positive (in all rabbits)
Gr up F	Un sensitized rabbit *macrophages* and other leukocytes	intra peritoneously	0/4	-	negative

plasmacells [4] It was also shown that the white opaque halo that appears surrounding the graft (during the course of a corneal transplantation when the opaque or clouding reaction is showing up) is also constituted by an analogous antigen antibodies complex precipitate

The production of these antibodies active at the corneal level has been long studied Remky [5] supposed that some cells of the connectival *corneal parenchyma* under the grafted antigen stimulus may become capable to sentisize immunoglobulins Nevertheless the lymphoid cells from the blood or lymphatic stream of the sclero corneal limbus or uvea or from regional lymphonodes or even the spleen are certainly involved in the production of antibodies The cloudiness of the corneal *transplant may* be *therefore considered as the final* consequence of this secondary accumulate of macrophages and of immunologically competent cells on the corneal limbus and of the subsequence cytotoxic effect of their specifically sentisized immunoglobulins [6] Parks & C have studied the immunologically competent cells at a limbus level in the days that follow a *transplantation when a local typical reaction of the hypersensitivity* type is demonstrable They have shown after few hours a first comparison of polymorphonuclear cells and of round lymphoid cells Then when humoral antibodies may be detected in the aqueous or in the serum of the recipient the cellular infiltrate of the limbus appears formed mainly by plasmacells and *lymphocytes When the antigen was labelled with a fluorescent tracer* fluorescence was visible inside the cytoplasma of three plasmacells Leibowith & Parks [28] 3 and 5 days after transplantation removed some of these lymphoid cells from the limbus for cultivation Fourteendays afterwards these cells produced antibodies *in vitro* Probably the final cloudiness of a corneal graft is *determined by an opsonizing effect and/or a more specifical* and direct cytotoxic effect of these immunoglobulins Recently Ehrlich & Halbert [29] have demonstrated that antiserum produced in the duck against pooled rabbits corneas exhibit cytotoxic effects on rabbits corneal epithelium or endothelium cells grown *in vitro*

In preceding *experiments we had shown that an interlamellar* chicken corneal graft remains transparent if it was transplanted into a cornea of a Rx irradiated rabbit [6] The grafted heterologous cornea under these conditions usually takes a long time Histologic examinations effected in these eyes 3 months after transplantation showed that epithelial cells of a chicken corneal *graft were still alive These cells multiplied* and covered the pocket obtained between the lamellae of recipient rabbit corneal parenchyma Under these conditions any immediate or very precocious effect consequent to a passive administration of antibodies or immunologically active cells may *be therefore* considered directly consequent and specific The results of our present experiments indicate that a on intravenous administration of a large amount of homologous humoral immunoglobulins specific against chicken corneal extracts

provocated a very early cloudiness of a long transparent inter lamellar chicken corneal graft in rabbits The opacification was followed by typical signs of a classical transplant reaction i e Wesseley s ring and neovascularity in the recipient cornea The intravenous administration of immunologically competent lymphocytes did not produce any early effect i e 7 days after the challenge whereas when a large mixed population of lymphonodes and spleen macrophages and other polymorphonuclear leukocytes was injected intra peritoneously the grafts clouded with typical signs of an immune reaction The corneal opacification did not happen within few hours as when antibodies were injected intra venously but it necessitated some days from the challenge In these last animals antibodies against chicken corneal extract were detected at the seventh day after the challenge since specific antibodies against chicken corneal extract were not detected before the challenge these results may suggest a direct partecipation of the recipient in the synthesis of antibodies Nevertheless presensitized antibodies had been also carried on the surface of the same passively administered macrophages since recent evidences in literature suggest the possibility of an opsonizing and may be also cytotoxic activity of these cytophilic antibodies[20 21] we cannot exclude that these antibodies had also been *involved* in the corneal opacification reaction

It is known that the antibodies production of the recipient may be conditionated from its capacity to recognize the anti genic stimulation of the graft However in experiments carried out *in vivo* it was shown many times that the formation of immunoglobulins is relatively indipendent of the *postoperative behaviour* of the graft Thus in some cases in which the inflammatory reaction was relatively less marked the formation of immunoglobulins was as high as in the other animals with strong tissue reactions

These evidences may indicate that different classes of immunoglobulins may be produced during the immune response to a corneal transplantation and that their specific biological effects may be different Moreover these *evidences may* also indicate that also non immunogenic factors such as the anatomical struc*ture of the* cornea or its avascularity must play an important role in the fate of an inter lamellar corneal graft The thick connective tissue of the corneal parenchyma may in fact repres nt an impredictable and important filter and hinder the passage of calls of the diffusibility of antigenic materials

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No more than 1 per cent of adult patients with general toxoplasmosis have any ocular signs and symptoms and it is even doubtful whether the uveitis or cicatrices in the fundus in these cases are due to Toxoplasma

A diagnosis of toxoplasmic uveitis in newborn is made on the basis of cere bral signs (calcification disclosed by X ray) ophthalmological signs and po sitive reaction to Toxoplasma

In adults it is difficult or impossible to decide whether uveitis is due to toxo plasmosis The information obtained from serological tests is poor because the toxoplasmic reactions very often are positive in normal adults

Detection of Toxoplasma in biopsy specimen or on enucleated eye may be difficult Toxoplasma may be confounded with necrotic cells Toxoplasma may occur in an encapsulated form with several hundred paratites within a capsule produced by themselves This finding permits a definite diagnosis

Inoculation tests on animals will likewise establish the diagnosis

Toxoplasma has been observed in aqueous humour aspirated vitreous body and subretinal fluid

Only few positive findings are available Consequently our knowledge of uveitis of definite toxoplasmic origin in adults is very slight With our present knowledge we are hardly justified in setting up specific criteria *characterizing* Toxoplasma induced uveitis in adults

By comparing the adult form with the *congenital the result* has been arrived at that in particular central retinochoroiditis must be characteristic of toxoplas mosis Relapses along the border are frequent in some instances in the form of satellites Others have pronounced that juxtapapillary *choroiditis (Edmund Jensen)* and even peripheral disseminated choroiditis may be due to Toxoplas ma *(Hogan)* Primary anterior uveitis due to Toxoplasma has never been ob served *(Hogan 1964 Duke Elder)*

The diagnosis depends in practice on uveitis type and serology Several se rological tests exist of which the dye test is the one most frequently employed (Sabin Feldman s neutralisation test)

For this test living Toxoplasma is mixed with the patient s serum and methy lene blue

Methylene blue normally stains Toxoplasma If added serum contains anti body against Toxoplasma the Toxoplasma is not stained The cytoplasm re mains unstained

The reaction depends on accessory factors the quality of the dye and the properties of the Toxoplasma strain used *(Straub Woods)*

The results from different laboratories are not direct comparable On the

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ENDOGENOUS UVEITIS

IV Toxoplasmosis

BY

M S NORN

Toxoplasmosis is produced by *Toxoplasma gondii* a 5 7 μ long unicellular obligate parasite with a central nucleus and banana shaped cytoplasm It is Gram negative

This parasite was first detected in a North African rodent gondi in *1908* Later it was found in wild hares in Denmark (*8 per cent of 2411 naturally* dead hares *Magnus Christiansen)* It has since been shown to occur frequently in domestic animals and humans *(Siim)*

The route of infection is unknown but especially the respiratory passages are suspected Contamination from man to man is also *likely*

It is a well known fact that in man Toxoplasma may cause a congenital disease affecting the brain and eyes *via* a maternal generally non recognized infection

The infection is primarily retinal The eye may present a central retinochoroiditis In some instances the whole eye is affected so much as to become phthisic

The first case of congenital ocular affection in this country was examined by *J Brons* and described by *I Boesen* in 1948

It is more doubtful whether toxoplasmosis may lead to uveitis in adults The question has been discussed whether a possible toxoplasmic uveitis in adults is due to recurrence of a not previously recognized or previously invisible congenital choroiditis or to a toxoplasmosis of the eye acquired at the adult age

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The reaction depends on accessory factors the quality of the dye and the properties of the Toxoplasma strain used *(Straub Woods)*

The results from different laboratories are not direct comparable On the

other hand the reaction must be regarded as specific as no other parasites give occasion to positive reaction *(Sum)*

The complement fixation test has been employed in only few series of uveitis cases This is likewise specific The reaction takes longer to become positive than that to the dye test and wears off sooner

The dye test gives positive reaction after 2 4 weeks and the complement fixation test after 3 7 weeks *(Sum)* The dye reaction becomes normal after 2 4 years and the complement fixation reaction after 1 2 years *(Straub)*

This difference between the two reactions may be due to the complement fixation test being less sensitive than the dye test or to the latter reaction depending on a different antibody

To assess the possible occurrence of Toxoplasma induced uveitis the frequencies calculated for existence of Toxoplasma antibodies in fairly large series of uveitis cases have been reported

Perkins obtained a positive dye test in 86 9 per cent of 258 patients with acute posterior uveitis against only 62 3 per cent of 896 patients with acute anterior uveitis Using the complement fixation test posterior uveitis gave 13 9 per cent positive against anterior uveitis 9 4 per cent

Perkins is therefore of the opinion that only posterior uveitis may be due to toxoplasmosis This is in agreement with the finding in newborn infants in whom anterior uveitis if present at all must be secondary to posterior uveitis Perkins control series is not quite reliable being older than the uveitis series Perkins is therefore inclined to let the anterior uveitis cases act as controls

Hogan (1951) and *Paul* seem to have found no difference between anterior and posterior uveitis in this respect Hogan therefore confined himself to studying the dye positive cases affording clinical suspicion of toxoplasmosis These were in his opinion always cases of posterior uveitis *(Hogan* 1964)

Uveitis series ought to be compared with normal series with regard to the incidence of a positive dye titre Unfortunately the figures stated for normal series differ very considerably According to *Duke Elder* there are about 30 50 per cent positive in normal series but the values stated in the literature range from 2 to 75 per cent *(Paul Sum)*

These enormous differences may be due to the various laboratories employing different procedures and to unequal geographical distribution of the parasite

The incidence of positive dye tests rises from zero at birth to a high value at the age of 20 from which age it remains at this high level *(Weekers)*

The incidence of positive reactions must however be supposed to fall with increasing age after a certain maximum because toxoplasmosis is an infection generally acquired early in life *(Sum* personal communication)

Toxoplasmosis involving the eye might be conceived to cause greatly raised titres This need not be so however Hogan only found a positive value in completely undiluted serum from a patient with toxoplasmosis of the eye The

diagnosis was verified at autopsy which disclosed myriads of toxoplasmic cysts

This may be accountable for by the fact that choroiditis is an inflammation which comprises a very small area and therefore gives occasion to such negligible antibody production that this does not manifest itself by any appreciable rise in titre (*Perkins*) This presupposes that the patient is not particularly allergic to toxoplasma

Hogan concluded that the titre value is of little diagnostic significance

Present Material

During the past 10 years uveitis patients have been examined as a routine for toxoplasmosis in our Department

The report comprises all uveitis patients with active uveitis referred to the Ophthalmic Out Patients Department *Kommunehospitalet* during the period of 1958 1968

The material has been assessed clinically (*Norn* A) prognostically (*Norn* B) and with regard to serological antistreptococcal reactions (*Norn* C)

The series reported comprises just over 400 patients of whom 245 were subjected to dye test and complement fixation test for Toxoplasma The tests were made in the Toxoplasmosis Section *Statens Seruminstitut* (Head I Chr Siim)

Aage and sex

The results of the dye tests made in dilutions 1 10 1 50 1 250 etc are shown in table I

The lowest dilution regarded as positive is that of 1 10

The dye test gave positive reaction in 56 per cent of the total uveitis series

The test gave fairly equally raised values in all age groups More particularly there were no signs of a decrease in positive reactions in the relatively old age classes

A positive reaction was found in 60 *per cent* of females and 51 per cent of males perhaps with a preponderance of females in the fairly old age classes (table I)

At *Statens Seruminstitut* they are collecting and examining a normal material that is direct comparable with the present uveitis material examined in the same laboratory Unfortunately the *material* is not yet available but Dr *Siim* has kindly studied the values obtained for the present series He judged that the figures were higher than may be expected in a normal material More particularly he found it remarkable that the incidence of raised values remained high in the old age groups

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Toxoplasmosis involving the eye might be conceived to cause greatly raised titres This need not be so however Hogan only found a positive value in completely undiluted serum from a patient with toxoplasmosis of the eye The

highest value recorded in this series and generally not regarded as particularly high

It is remarkable that six of these seven cases also had a positive complement fixation test

The complement fixation test was only found positive in association with a positive dye test and most frequently in patients with fairly high dye test titres (table II)

The complement fixation test was positive in a total of 9 per cent of the uveitis series

Uveitis types

Table III shows that the dye test gave strikingly high values in cases of acute fibrinous iritis hypopyon panophthalmia as well as juxtapapillary and peripheral choroiditis

The dye test was surprisingly seldom positive in cases of chronic iritis and central choroiditis There was however no statistical difference between the various groups

The dye test was positive in 54 per cent of the cases of posterior uveitis and 56 per cent of those of anterior uveitis

This is in disagreement with Perkins observation of a higher frequency of positive dye tests among patients with posterior uveitis

The dye test was not particularly often positive in central choroiditis either

Table III

Serological toxoplasmosis tests in relation to different uveitis types a total of 245 cases

	dye test pos %	dye test ≧ 1 50 %	compl fixat test pos %	number of pts
acute fibrin iritis	61	24	10	49
non gran iritis	50	14	8	66
granulomatous iritis	69	21	11	19
hypopyon panophthalmia	71	43	29	14
chron iritis	40	15	5	20
central choroiditis	4	14	6	50
juxtapapillary chor	79	36	7	14
peripheral choroiditis	7	31	8	13
Total	56	20	9	245

Table I

Frequencies of positive dye titres among 245 uveitis patients Age and sex

age	toxoplasmosis % both sexes	toxoplasmosis % females	toxoplasmosis % males	number of patients
0–9	60	100	33	5
10–19	48	59	33	40
20–29	58	31	75	40
30–39	48	58	43	42
40–49	56	58	53	48
50–59	65	73	53	37
60–69	59	67	25	22
70–79	64	75	57	11
Total	56	60	51	245

By way of comparison it may be stated for instance that *Paul* found 45 per cent positive dye tests *Perkins* 67.4 per cent and *Straub* 80 per cent in uveitis series

In control series *Oksala* found 23 per cent, *Perkins* 22–29 per cent, and *Weckers* 60–70 per cent positive dye tests

In the present series the dye titre was most often of the lowest value (table II)

Hogan likewise found fairly low titre values rarely above 1:256

In the present series only seven patients had a titre value of 1:250 the

Table II

Titre value of dye test compared with reaction to complement fixation test. 136 positive dye tests (The complement fixation test gave the following values in 17 cases 1:2 in two 1:4 in two 1:8 and in one 1:16(32))

dye titre value	number of patients	positive complement fixation test number of patients
1:10	86	2
1:50	43	14
1:250	7	6
Total	136	22

with applanation tonometer and the cases with proper secondary glaucoma have been grouped under glaucoma The dye test was not more often positive in these cases

The reaction to the dye test bore no relation to the poorest visual acuity recorded during the course of the disease

In other words the frequency of complications seemed not to be increased among cases with a positive dye test.

General diseases

No correlation seemed to exist between rheumatic diseases (chronic rheumatoid arthritis sequelae of rheumatic fever Reiter's disease and spondylarthritis anchylopoietica) or focal diseases on one hand and a positive dye test on the other (table V)

Recurrence rate – bilateral occurrence

The recurrence rate is seen in table VI A positive dye test might be expected to occur chiefly in cases with many relapses because Toxoplasma tends to propagate with resulting rupture of the capsule and consequent spreading of Toxoplasma

However the figures showed no unquestionable correlation between a positive dye test and many relapses

Of the patients with more than four relapses 67 59 per cent reacted positively against only 51 per cent of the recurrence free There was no significant difference however between recurrence free and recurrent uveitis

The dye test was equally often positive among chronic and non chronic cases

Bilateral cases were not more often positive than unilateral

Table V

Results of toxoplasmosis dye test in patients with *articular* and focal diseases Of the total uveitis series 56 per cent were toxoplasmosis *positive*

	toxoplasmosis pos %	number of patients
chronic polyarthritis	45	11
spondylarthritis anchylopoiet	80	[illegible]
seq of rheumatic fever	40	5
Reiter's disease	[illegible]0	5
focal diseases	50	30

which is regarded as the most characteristic clinical form of toxoplasmic uveitis

The cases of positive dye test with titre values of 1:50 or higher have been tabulated (table III) These constituted 20 per cent of the entire uveitis series

The distribution over the various types is in fair agreement with the distribution of positive dye tests as stated above

Only seven out of 245 examined had a titre of 1:250

These seven cases are remarkable because clinically they corresponded fairly closely to the uveitis type we should expect to find in toxoplasmosis

Two of these patients were newborn infants one with microphthalmia and one with disseminated choroiditis

Three were under 20 years of age with central or paracentral choroiditis

Two were somewhat older 34 and 54 respectively The former had choroiditis under the optic disc and the latter juxtapillary choroiditis

Most of these cases were thus suspicious of toxoplasmosis of the congenital type

Ophthalmic complications

Different ocular disorders complicating uveitis have been set out in table IV

The result of the dye test seemed to bear no relation to occurrence of dilated retinal veins or periphlebitis

The dye test was not more often positive in the cases where the optic nerve was involved (hyperaemia indistinct disc margins)

The uveitis cases with a concurrent rise in pressure above 25 mm measured

Table IV

Complication and visual acuity in uveitis cases compared with the result of toxoplasmosis dye test (Sec glaucoma includes all cases in which a pressure above 25 mm with applanation tonometer was measured during the course of the uveitis)

	toxoplasmosis pos %	number of patients
periphlebitis dilated veins	60	75
papillitis	59	29
secondary glaucoma	55	31
poorest vision < 1/60	58	48
< 6/60	72	32
< 6/18	47	64
< 6/9	48	52
≥ 6/9	61	49
Total	56	245

This observation was not borne out in the present study and apparently no more in those of *Hogan* and *Paul*

A diagnosis of adult toxoplasmic uveitis must be corroborated in a more direct manner than by the dye test in serum

Remky and *Dedust* & *Witmer* studied the results of the dye test in aqueous humour by puncturing the chamber of patients with uveitis

A positive dye test in aqueous humour may be due to passage of antibody from the blood stream owing to breakdown of the blood aqueous humour barrier owing to uveitis no matter of which aetiology

To justify a diagnosis of toxoplasmic uveitis is has therefore been required that the titre is higher in aqueous humour than in blood (quotient > 1)

Dedust & *Witmer* concluded on the basis of *such studies that the number of* cases of unquestionable toxoplasmic uveitis does not exceed 10 per cent of all forms of uveitis

Remky estimated that 9 per cent of all uveitis *cases* and 20 *per cent* of all posterior uveitis cases are due to toxoplasmosis the quotient exceeding 1 in central choroiditis parapapillary and juxtapapillary choroiditis and in retinal periphlebitis

Chamber puncture is hardly an absolutely harmless procedure *Hogan do not* consider this procedure to be indicated He prefers to base the diagnosis on the result of the serological test combined with the clinical picture

In few cases only will it be possible to establish the *diagnosis to toxoplasmic* uveitis by inoculating samples of aqueous humour vitreous body or subretinal *fluid* or by finding characteristic toxoplasmic cysts in biopsy specimens

The age incidence of positive dye tests in serum noticed *in the present* series suggested existence of an adult form of toxoplasmic uveitis A corresponding control series has not yet been examined

Which conclusions can be drawn from the result of a serological test *for* toxoplasmosis in an uveitis patient?

A positive titre in a newborn infant or a child is evidence of presence of toxoplasmosis presumably congenital The eye disease is probably due to Toxoplasma In these cases the dye test will often *give* rather highly positive reactions and so will the complement fixation test The course of the disease can be followed by repeated serological tests

A positive dye test in an adult patient with uveitis shows that *the patient* has or has had toxoplasmosis probably of the clinically *silent* type The existing uveitis is unlikely to be due to Toxoplasma

Uveitis with a positive reaction to the dye test *runs* exactly the same course as uveitis with a negative reaction The dye positive and the dye negative cases are alike with regard to *recurrence* rate chronicity complications and *uveitis* types

Table VI

Toxoplasmosis test compared with course of uveitis recurrence rate bilateral occurrence Positive dye test in per cent

	toxoplasmosis pos %	number of patients
2 attacks of uveitis	56	61
3 4	56	41
5 6	67	15
≧7	59	17
chronic course	59	37
no recurrence	51	49
bilateral	57	115
Total	56	245

Discussion

The present investigation bore out the view that serological tests for toxoplasmosis are of importance in newborn and young individuals to diagnose congenital toxoplasmosis of the eye

In such cases the dye test often reveals a rather high titre and in addition a pathological reaction to the complement fixation test is frequent

Both tests are negative in young normal series

Toxoplasma has affinity at least in newborn to the cerebrum and to the projecting part of the brain constituted by the retina

Cerebral toxoplasmosis is rare in adults In most cases the parasites reach no further than the lymph glands where they give rise to a febrile or asymptomatic lymphadenopathy (*Siim*)

It has been demonstrated both histologically and by experiments with inoculation from the vitreous body subretinal fluid etc that Toxoplasma may be found in the retina and choroid of adults

However in spite of numerous investigations it has not yet been clarified whether Toxoplasma in adults is a frequent cause of uveitis or whether perhaps equally rare as the adult cerebral form of toxoplasmosis

In the cases of uveitis we do not have the impression that the eye disease has been preceded by a general disease cerebral disorder or lymphadenopathy suggesting an acquired toxoplasmosis

Perkins inclined to the view that acute posterior uveitis often is due to Toxoplasma because he found the dye test to be more frequently positive in this disease than in anterior uveitis

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A negative dye test highly suggests that the patient s uveitis is not due to Toxoplasma This theory does not hold good in all cases however some having been described with definite ocular toxoplasmosis but no unquestionably positive dye test *(Hogan)*

At present the due test thus seems to give no information of practical importance in the individual uveitis case if the patient is an adult

It is to be hoped that better serological tests may give information of greater value (flocculation test fluorescence test)

Skin test for toxoplasmosis seems not to be more suitable than the serological tests

The discussion *on the possible toxoplasmic aetiology* of uveitis *in adults* is of more than theoretical interest because a treatment can be offered against a diagnosed toxoplasmosis

With our present knowledge we *must conclude that congenital toxoplasmosis with associated posterior uveitis* is an established nosologic entity which presumably may recur in the uvea several years after birth

Adult toxoplasmic uveitis does exist but its incidence is unknown and with the aids available at present the diagnosis can be made in very few cases only

Summary

245 unselected cases of endogenous uveitis were subjected to serological tests for toxoplasmosis

In 56 per cent there was found a positive dye titre (Sabin Feldman s neutralisation test) of not less than 1 10 but in only 3 per cent a titre of 1 250 or more The complement fixation test was positive in 9 per cent

A positive dye test seemed to be independent of age in the uveitis series

The reaction seemed to be independent of the recurrence rate bilateral occurrence and complications of the uveitis such as papillitis periphlebitis visual impairment and rise in intraocular pressure

Further the reaction seemed to be independent of the uveitis type *More* particularly is was not more frequent in relation to posterior uveitis *or central* choroiditis

Serological test is of value in newborn and children for disclosing toxoplasmic uveitis

In adult uveitis patients on the other hand serological test is of doubtful value *this being most often* positive with the same titres as in adults suffering from asymptomatic toxoplasmosis without ocular manifestations A negative test argues against toxoplasmic aetiology of uveitis

Perkins found a positive W R in three out of 653 uveitis cases and concluded that active syphilis seldom is the cause of uveitis in England

Oksala saw 3 per cent syphilitic among 100 uveitis cases *Leira* found a positive W R in 2 5 per cent In two of the six patients with positive reaction no other cause of the uveitis was detectable than the diagnosed syphilis

Leira concluded that to day syphilis seems to be no significant aetiological factor The syphilitic uveitis may be difficult to diagnose because a positive seroreaction may be seen in a patient with uveitis which possibly may have a different cause

Certain clinical features may however argue in favour of a syphilitic aetiology

In the presence of iritis there may be found papules nodes or circumscribed vascular glomera (iritis roseata)

In diffuse choroiditis exudates perivascularly and round the optic disc may be characteristic In tertiary syphilis a generalized uveitis may be so pronounced as to lead to phthisis *(Woods)*

The syphilitic uveitis may however be quite uncharacteristic and must be evidenced by positive serology and improvement in response to specific therapy possibly with a transitory exacerbation 10 16 hours after started treatment (*Jarisch Herxheimer s* reaction)

The influence of *gonorrhoea* on the development of uveitis may be difficult to assess In previous publications urethritis with associated uveitis and possibly also arthritis was claimed to be of gonorrhoeal origin Modern writers on the other hand distinguish between gonorrhoeal urethritis and non specific urethritis The latter may be found as a manifestation of Reiter s disease and spondylarthritis anchylopoietica *(Perkins)*

Perkins found three positive gonococcal complement fixation reactions (G R) among 653 uveitis patients

Vesterdal diagnosed gonorrhoeal uveitis in 9 4 per cent all presenting fibrinous or subacute iritis

Out of 14 with positive G R in Vesterdal s series five were new diagnosed

Haarr found 17 gonorrhoeal cases among 252 men with acute iridocyclitis (11 gonorrhoeal cases among 149 with spondylarthritis anchylopoietica)

Leira found a positive G R to be almost equally frequent among uveitis patients (5 3 per cent) and a corresponding control group (5 8 per cent) In *Leira s* opinion the G R is of no importance in uveitis It may even lead one astray For ophthalmological clinical work it would probably be best to drop it

A typical gonorrhoeal uveitis will manifest itself by iritis with a large exudate and possibly blood in the chamber *(Perkins)* Other types may however very well be found such as simple iritis plastic iritis with a tendency to synechiae suppurative iritis whereas choroiditis is rare The iritis frequently recurs and is often bilateral

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ENDOGENOUS UVEITIS

V Laboratory Tests
(W R G R E S R S A T Hb %)

BY

M S NORN

The present report comprises the results of various laboratory tests made on a series of uveitis patients seen between 1958 and 1968 in this Department of Ophthalmology which serves an urban population of 700 000 inhabitants

In previous papers I reported on the clinical aspects and classification of the series (Norn A) recurrence rate and other prognostic criteria (Norn B) serological anti – streptococcal reactions (Norn C) and serological tests for toxoplasmosis (Norn D)

In this final report the results are given of serological tests for syphilis (W R) and gonorrhoea (G R) erythrocyte sedimentation rate (E S R) streptococcus agglutination test (S A T) and haemoglobin percentage (Hb %)

The venereal diseases play a certain role in the aetiological reflections concerning uveitis It is very important to subject a venereal disease to specific treatment

Syphilis was formerly stated to be the cause of uveitis in about 20 per cent *(Leira)* The diagnostic criteria are debatable however *(Duke Elder)*

In recently published series of uveitis cases only few per cent are of syphilitic origin

Lund found no instance of positive W R among 88 cases of chronic uveitis

Vesterdal noticed 4 6 per cent syphilitic among 350 patients with uveitis Among these one out of 14 positive W R was unexpected

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In the remaining five cases fibrinous or subacute iritis was seen which had developed from 1 to 20 years after the syphilis

In the present series a positive W R did not give the impression of being related to any definite iritis type More particularly there were found no cases of nodose iritis in this group

Specific treatment was given in the cases where the venereologist found indication for such

Nevertheless recurrence was notice in five of the eight uveitis cases with a positive W R The relapses ranged in number from two to twelve One patient developed a chronic course after four relapses

This may suggest that these cases were not all of syphilitic origin

It is perhaps reasonable to suppose that only the three recurrence free cases had a syphilitic aetiology These included the two with neurosyphilis

This gave a syphilitic aetiology in 1 per cent of the total uveitis series under review

In spite of this low percentage testing of the W R must still be indicated in relation to uveitis because a positive reaction may disclose a *not previously* recognized syphilis (cf the neurosyphilis diagnosed in an elderly woman of the present series)

Gonococcal Complement Fixation Reaction (G R)

The G R was found to be positive in 11 patients or 3 *per cent of* the total uveitis series

In four cases competing causes of uveitis were found two with a positive W R one with sinusitis and one with previous rheumatic fever and current spondylarthritis anchylopoietica

In three of the remaining seven cases (2 per cent of the total *uveitis series*) a gonorrhoeal aetiology was less likely because these patients had choroiditis

The four others (1 3 *per cent of* the total series) probably had gonorrhoeal uveitis two *with fibrinous* iritis and two with subacute nongranulomatous iritis One patient also had arthritis

The G R thus rarely gives information on *gonorrhoeal* aetiology of uveitis

A *history* og gonorrhoea was *given by* 15 patients (5 per cent of the total uveitis series)

A different possible cause of the uveitis was found in six cases (spondylarthritis anchylopoietica Reiter s disease *chronic rheumatoid* arthritis sequelae of rheumatic fever and sinusitis) In one case gonorrhoea did not develop till after the first attack of uveitis

The gonorrhoeal uveitis develops at the earliest 4 6 weeks aften the primary infection, in some instances simultaneously with arthritis, which however is not necessarily present

It may develop several years after the urethritis as late as 10 years after the primary infection

The G R test is not reliable The past history and direct demonstration of gonococci are therefore important

Present Investigations

A previously published series of uveitis patients *(Norn)* was subjected to the serological tests for venereal diseases and the other laboratory tests

The original series comprised 449 patients

W R was tested in 322 of these cases G R in 320 E S R in 322 S A T in 257, and Hb % in 222

These tests were made as a routine on no definite clinical indication or suspicion The tests for S A T and Hb % were only made on the patients seen within the latter part of the investigation period

The serological tests were all made at *Statens Seruminstitut* while the tests for E S R and Hb % were made at the Central Laboratory *Kommunehospitalet*

Wassermann Reaction (W R)

In no more than one case was a positive W R noticed in a patient with not previously recognized syphilis

The W R was positive in a total of ten patients of whom however two gave only unspecific reaction One of these patients was subjected to treponema pallidum immobilisation test (T P I Nelson) which was negative

One patient displayed competing causes of the uveitis (spondylarthritis ankylopoietica and at the same time a positive G R)

Then seven cases are left (2 2 per cent of the whole uveitis series) with a possible syphilitic aetiology Two of these had neurosyphhilis with a verified positive T P I

One of the neurosyphilis cases was only recognized because the W R was found positive on routine testing owing to iritis (a woman aged 62) The other patient with neurosyphilis presented chronic fibrinous uveitis with associated retinal detachment

Table I

Pathological erythrocyte sedimentation rate (E S R) in the total uveitis series (E S R values above 10 mm in men and 15 mm in women are regarded as raised)

	raised E S R %	E S R > 30 %	number of patients
females	52	25	161
males	52	17	161
Total	52	21	322

Uveitis Types

The E S R was very often raised among the cases of acute fibrinous iritis (84 per cent) being even above 30 mm in about one third of the cases (table II)

Among the patients with subacute non granulomatous iritis the number with a raised E S R was as in the total uveitis series (52 per cent)

Choroiditis was associated with a raised E S R in a surprisingly small number of cases (28 per cent) The incidence corresponded to that in *Leira's* control series

Table II

Pathological E S R values in different uveitis types

	raised E S R %	E S R > 30 %	number of patients
acute fibrinous iritis	84	37	74
non gran subac iritis	52	24	89
granulomatous iritis	60	8	25
hypopyon and panophthalmia	53	26	19
chronic iritis	39	11	28
central choroiditis	[illegible]	11	27
juxtapapillary choroiditis	7	0	15
peripheral choroiditis	33	13	15
choroiditis Total	28	9	87
Total	52	21	322

Fight cases are left (2 1 per cent of the total series) with a likely gonorrhoeal aetiology though negative G R

One of these patients had urethritis uveitis and gonorrhoeal ophthalmoblennorrhoea with Gram negative intracellular diplococci demonstrated in conjunctival smears

One patient presented iritis with hyphaema four acute fibrinous iritis and two subacute iritis

Most of the patients with iritis experienced numerous relapses

There were no cases of choroiditis

This report bears out the view that the past history is important Gonorrhoeal uveitis was evidenced anamnestically in 2 1 per cent of all the uveitis cases, while the C R afforded evidence of this aetiology in another 1 3 per cent

A total of 8 per cent of the whole uveitis series gave a history of gonorrhoea or had a positive G R at the time of examination

Gonorrhoeal uveitis was evidenced in 3 per cent of all the uveitis cases Gonorrhoeal uveitis with associated arthritis was found in one case only (0 3 per cent)

Erythrocyte Sedimentation Rate (E S R)

In the present series above 15 mm/1 hour for women and above 10 mm/1 hour for men were chosen as pathological E S R values

With these limits allowance has been made for the fact that women more often than men have a slightly raised value

Leira chose the same lower limits for pathological values The two uveitis series are therefore direct comparable

Total Series

A raised E S R was recorded in just over half of the uveitis series (52 per cent)

Using the chosen lower limits there was no difference between females and males but higher E S R values (above 30) seemed to be more frequent among the women (table I)

Leira likewise found pathological E S R values in about half of his uveitis cases (48 6 per cent) against in only third of the control series (31 9 per cent) The sedimentation rate is thus surprisingly often raised in cases of uveitis

Bjork found a raised E S R in about half of the cases *Vesterdal* in 38 per cent *Oksala* in 79 per cent of acute uveitis cases and 71 per cent of chronic uveitis cases

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males	5[illegible]	17	161
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hypopyon and panophthalmia	53	26	19
chronic iritis	39	11	29
central choroiditis	3[illegible]	11	57
juxtapapillary choroiditis	7	0	15
peripheral choroiditis	33	13	15
choroiditis Total	[illegible]8	9	87
Total	5[illegible]	[illegible]1	3[illegible]2

Fight cases are left (2 1 per cent of the total series) with a likely gonorrhoeal aetiology though negative G R

One of these patients had urethritis uveitis and gonorrhoeal ophthalmoblennorrhoea with Gram negative intracellular diplococci demonstrated in conjunctival smears

One patient presented *iritis with hyphaema four acute fibrinous iritis and* two subacute iritis

Most of the patients with iritis experienced numerous relapses

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This report bears out the view that the past history is important Gonorrhoeal uveitis was evidenced anamnestically in 2 1 per cent of all the uveitis cases while the C R afforded evidence of this aetiology in another 1 3 per cent

A total of 5 per cent of the whole uveitis series gave a history of gonorrhoea or had a positive G R *at the time of examination*

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a correlation between the E S R and the severity of the uveitis a fact which seems not to have been mentioned previously

On the other hand there seemed to be no correlation between a raised E S R and a rise of the intra ocular pressure of above 25 mm measured by applanation tonometry or proper secondary glaucoma No correlation was noticed between a raised E S R and occurrence of dilated retinal veins periphlebitis or involvement of the optic nerve

General Diseases

It was not surprising that the E S R was raised in the cases where the patient in addition to uveitis suffered from a general disease which is known by experience to give a raised E S R (table IV)

The E S R was found raised in the presence of joint diseases (chronic rheumatoid arthritis spondylarthritis anchylopoietica sequelae of rheumatic fever and Reiter s disease) and perhaps focal diseases and tuberculosis

The raised E S R could be explained by presence of a recognized general disease in 55 cases at most but was found in 168 of the total number of uveitis patients In other words the raised E S R could not be accounted for in at least 113 cases i e in just over two thirds of all the uveitis cases with a raised E S R

Prognosis

The chance of recurrence was seen to be greater in cases with a raised E S R

Table IV

Pathological E S R values in uveitis with associated general diseases

	raised E. S R %	E. S R > 30 %	number of patients
spondylarthritis anchylopoiet	77	77	13
seq of rheumatic fever	80	40	10
Reiter s disease	83	50	12
Boeck s sarcoid	30	10	10
tuberculosis syphilis gonorrhoea	73	[illegible]	40
focal diseases	66	21	33
other general diseases	40	10	20
Total	[illegible]	[illegible]	[illegible]

Vesterdal likewise noticed a raised E S R in many cases of acute fibrinous iritis (52 per cent against 38 per cent of the total series) *Leira* found the E S R to be raised particularly in cases of acute iritis attending spondylarthritis anchylopoietica (91 per cent of men)

Perkins found the E S R to be most frequently raised in acute anterior uveitis and in acute and chronic generalized uveitis

The unequal clinical classifications and the different limits chosen for pathological E S R values render direct comparison of the various series impossible The investigations suggest however that the E S R most often is raised in cases of acute iritis in particular the fibrinous form

A raised E S R indicates an abnormality of the serum proteins in these patients Oksala also observed an abnormal serum electrophoresis pattern in uveitis

This suggests that certain uveitis types form part of some general disease or other as the eye disease is unlikely alone to alter the composition of the serum proteins

Ophthalmic Complications

A pronounced iritis will result in a greatly impaired vision at the culmination of the disease whereas mild iritis will cause only a minor visual impairment

The poorest vision recorded during the course of uveitis has been set out in table III The figures go to show that patients with a raised E S R experienced the gravest visual impairment at the culmination of the disease This suggests

Table III

Pathological E S R values in ophthalmic complications and in relation to poorest visual acuity recorded during course of uveitis

	raised E S R %	E S R > 30 %	number of patients
periphlebitis and dilat veins	56	18	88
papillitis	53	11	36
secondary glaucoma	59	27	56
vision poorest			
< 1/60	66	32	76
< 6/60	51	16	43
< 6/18	49	17	81
< 6/9	56	24	63
≥ 6/9	36	19	59
Total	52	21	322

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focal diseases	66	21	33
other general diseases	40	10	[illegible]
Total	[illegible]	[illegible]	[illegible]

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< 1/60	66	32	76
< 6/60	51	16	43
< 6/18	49	17	81
< 6/9	56	24	63
≥ 6/9	36	12	59
Total	52	21	322

Present Investigations

A positive S A T was found in 12 out of 257 tested uveitis patients (5 per cent) seven females and five males

The number of S A T positive patients did not exceed that to be expected in a normal series tested by the same method in the same laboratory *Statens Serumınstitut (Faber* personal communication)

Four of the 12 positive patients had a general disease two chronic rheumatoid arthritis and two Reiter s disease The patients with spondylarthritis anchylopoietica rheumatic fever and focal disease had a negative S A T

The antistreptolysin titre was positive in two of the 12 S A T positive cases The antistreptohyaluronidase titre was likewise positive in two cases This corresponds approximately to the distribution in the remaining series

The S A T reaction seemed to be independent of the uveitis type (acute fibrinous iritis 7 per cent subacute iritis 4 per cent nodose iritis none chronic iritis 4 per cent choroiditis 6 per cent total uveitis series 5 per cent S A T positive)

Complications were not particularly frequent among the S A T positive No relationship was seen between S A T positivity on one hand and recurrence rate bilateral occurrence chronicity or poorest vision during the course of uveitis on the other hand

In other words the S A T reaction gives no aetiological topical or prognostic information of value in cases of uveitis The reaction is rarely positive and seems to be of no interest in such cases

Woods is likewise of the opinion that the S A T reaction is of *no* value in relation to iritis

Haemoglobin percentage (Hb %)

Simple anaemia is often present in association with joint diseases both chronic *rheumatoid* arthritis spondylarthritis anchylopoietica and rheumatic fever

In the present report values below Hb 100 % (below 14 8 g %) for males and below Hb 90 % (below 13 3 g %) for females were recorded as anaemia

In the uveitis series under review just over one third (36 per cent) had anaemia women a little more often than men (39 and 33 per cent *respectively*)

Iritis Types

It is seen in table VI that anaemia was most frequent among cases of acute and subacute iritis There was no *difference in this* respect between acute fibrinous iritis subacute non granulomatous iritis and granulomatous iritis

than in cases with a normal value Table V shows the number of cases with a raised E S R to increase with increasing *number of relapses*

Bilateral cases more often had raised E S R values than unilateral The difference is statistically significant

Streptococcus Agglutination Test (S A T)

The S A T is not a test aiming specifically at *disclosing streptococci It acts* by an alteration of the serum proteins which in pathological cases causes agglutination of haemolytic streptococci

The reaction is only characterized as positive if there is agglutination of intensity 2 or 3 in the first tube corresponding to a serum dilution of 1 20 The *intensity* of the agglutination is given in grades 4 3 2 1 and 0

The test is often positive in cases of chronic rheumatoid arthritis (in nearly 80 per cent *Kalbak)* on a line with other rheumatic factors The S A T is negative *in spondy*larthritis anchylopoietica and rheumatic fever *(Woods)*

Kalbak found only few positive tests among normals (1 5 per cent of 64 donors)

Table I

Pathological E S R values in uveitis cases Recurrence rate chronicity bilateral occurrence

	raised E S R %	E S R > 30 %	*number of* patients
2 attacks	42	17	[illegible]
3–4 attacks	57	16	49
5–6 attacks	59	22	[illegible]
≥ 7 attacks	72	34	32
chronic course	45	16	42
no recurrence	52	28	96
bilateral	61	24	154
unilateral	44	18	168
Total	52	21	322

Table VII

Incidence of anaemia among patients with ophthalmic complications and at lowest visual acuity during course of uveitis

	anaemia %	number of patients
periphlebitis or dilated veins	28	69
papillitis	35	23
secondary glaucoma	39	38
vision poorest		
< 1/60	44	45
< 6/60	37	27
< 6/18	31	54
< 6/9	29	49
≥ 6/9	38	47
Total	36	222

Table VIII

Incidence of anaemia among patients with general diseases in association with uveitis

Incidence of anaemia in relation to recurrence rate chronicity and bilateral occurence

	anaemia %	number of patients
chron rheumatoid arthritis	58	12
spondylarthritis anchylopoietica	[illegible]	4
seq of rheumatic fever	50	6
Reiter's disease	86	7
Boeck's sarcoid	13	8
tuberculosis syphilis gonorrhoea	40	[illegible]
focal disease	[illegible]	23
other general diseases	64	9
2 attacks	36	56
3–4 attacks	[illegible]	34
5–6 attacks	[illegible]	33
≥ [illegible] attacks	[illegible]	18
chronic course	[illegible]	6
no recurrence	39	0
bilateral cases	39	109
Total	[illegible]	[illegible]

Table VI
Incidence of anaemia among patients with different uveitis types (Hb values below 100 % 14 8 g % for men and below 90 % 13 3 g % for women are regarded as anaemia)

	anaemia %	number of patients
acute fibrinous iritis	44	45
subacute non gran iritis	42	66
granulomatous iritis	42	19
hypopyon and panophthalmia	55	11
chronic iritis	28	18
central choroiditis	21	38
juxtapapillary choroiditis	20	10
peripheral choroiditis	13	15
Total	36	222

Anaemia seemed to be rarer in chronic iritis and was strikingly rare in all forms of choroiditis

The difference between non chronic iritis (44 per cent) and choroiditis (19 per cent) is statistically significant

This result is remarkable and raises suspicion that acute and subacute iritis more often are associated with a general disease than choroiditis

The finding is reminiscent of the result of the E S R investigation However especially the group of acute fibrinous iritis showed more pathological values than that of subacute iritis which again had a greater number of pathological values than that of choroiditis

Ophthalmic Complications

There was found no unquestionable correlation between occurrence of anaemia and the poorest visual acuity recorded during the course of uveitis

Anaemia was not more frequent among uveitis patients with periphlebitis dilated veins involvement of the optic nerve or a raised intra ocular pressure on account of the uveitis (table VII)

General Diseases

The incidence of anaemia among patients with uveitis and associated general disease is shown in table VIII

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≥ 6/9	38	47
Total	36	2[illegible]2

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focal disease	5[illegible]	23
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chronic course	[illegible]7	26
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General Diseases

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Department This shows that veneral diseases still are of topical interest within ophthalmology

It is important to diagnose venereal uveitis partly because specific antibiotic treatment should be instituted as early as possible and partly owing to the risk of transmission.

Hence W R and G R tests continue to be indicated in cases of uveitis

The present investigation showed that testing of the E S R is of value in uveitis partly to throw some light on a possible attending general disease especially joint disease and partly for prognostic reasons as a raised E S R is indicative of a severer course a raised recurrence rate and a tendency to bilateral occurrence

Anaemia was frequent in cases of acute subacute iritis and rare in choroiditis These findings suggest that acute fibrinous iritis and subacute iritis often are accompanied by a general disease a disease which however is diagnosable in only few cases of uveitis

The streptococcus agglutination test is rarely positive This probably indicates that chronic rheumatoid arthritis even in an atypical form very seldom is associated with uveitis

In cases of uveitis it is evidently other rheumatic diseases that must be considered (spondylarthritis anchylopoietica rheumatic fever Reiter s disease)

Conclusion

The series under review originally comprising 449 uveitis patients seen within the 10 year period of 1958 1968 allows of various conclusions on the basis of this and previous reports (*Norn* A D)

These incomplete conclusions must be considered in the light of our present knowledge of uveitis and the methods available at present for routine examinations

The clinical classification of the series of uveitis cases may be criticized The results suggest however that it is correct to isolate the *acute fibrinous iritis* as a special type

Fibrinous iritis is characterized by chiefly affecting fairly young men

Fibrinous iritis is the type most frequently associated with joint diseases of any kind though especially spondylarthritis anchylopoietica.

Papillitis strikingly rare in cases of fibrinous iritis A rise of the intra ocular pressure during the course of the disease is relatively rare compared with that in subacute iritis

As might be expected anaemia was frequent in relation to joint diseases (Reiter's disease chronic rheumatoid arthritis sequelae of rheumatic fever) Focal diseases were also frequently accompanied by anaemia The number of patients with spondylarthritis anchylopoietica was too small to disclose a possible frequent occurrence of anaemia

Recurrence Rate

The frequency of anaemia showed no unquestionable correlation to the number of relapses There was no difference between unilateral cases and such as were or later became bilateral (table VIII)

Unlike the F S R the haemoglobin percentage cannot be used as a prognostic sign Uveitis with associated anaemia may run exactly the same course as uveitis without anaemia

According to *Perkins* the haemoglobin percentage is of no particular interest in uveitis In the persent series however anaemia was found to be strikingly frequent among patients with acute fibrinous iritis subacute iritis and nodose iritis suggesting that these diseases often form part of general diseases perhaps especially joint diseases

Anaemia was rare in the cases of choroiditis this form being evidently not accompanied by such general diseases

Signs of a general disease in the forms of anaemia and/or a raised L S R were noticed in 67 per cent of the total uveitis series

Discussion

It is difficult to determine how many cases of uveitis are due to a venereal disease The seroreactions anamnestic data and the clinical picture suggest that of the uveitis cases under review 1 per cent were due to syphilis and 3 per cent to gonorrhoea

The figures are not fully reliable however partly because uveitis of a different aetiology may very well occur in patients with a positive venereal seroreaction and partly because venereal uveitis may be found in seronegative cases This is evident from the present series where C R negative cases of possibly gonorrhoeal uveitis were in the majority and also from the literature where cases of seronegative syphilitic uveitis have been described *(Aronson et al)*

In spite of the unreliable percentage numbers stated veneral uveitis must be supposed to be rare at present in this country

S Lorentzen recently described a case of syphilitic optic neuritis seen in this

Department This shows that veneral diseases still are of topical interest within ophthalmology

It is important to diagnose venereal uveitis partly because specific antibiotic treatment should be instituted as early as possible and partly owing to the risk of transmission.

Hence W R and G R tests continue to be indicated in cases of uveitis

The present investigation showed that testing of the E S R is of value in uveitis partly to throw some light on a possible attending general disease especially joint disease and partly for prognostic reasons as a raised E S R is indicative of a severer course a raised recurrence rate and a tendency to bilateral occurrence

Anaemia was frequent in cases of acute subacute iritis and rare in choroiditis These findings suggest that acute fibrinous iritis and subacute iritis often are accompanied by a general disease a disease which however is diagnosable in only few cases of uveitis

The streptococcus agglutination test is rarely positive This probably indicates that chronic rheumatoid arthritis even in an atypical form very seldom is associated with uveitis

In cases of uveitis it is evidently other rheumatic diseases that must be considered (spondylarthritis anchylopoietica rheumatic fever Reiter s disease)

Conclusion

The series under review originally comprising 449 uveitis patients seen within the 10 year period of 1958 1968 allows of various conclusions on the basis of this and previous reports (Norn A D)

These incomplete conclusions must be considered in the light of our present knowledge of uveitis and the methods available at present for routine examinations

The clinical *classification* of the series of uveitis cases may be criticized The results suggest however that it is correct to isolate the *acute fibrinous iritis* as a special type

Fibrinous iritis is characterized by chiefly affecting fairly young men

Fibrinous iritis is the type most frequently associated with joint diseases of any kind though especially spondylarthritis anchylopoietica

Papillitis strikingly rare in cases of fibrinous iritis A rise of the intra ocular pressure during the course of the disease is relatively rare compared with that in subacute iritis

Patients with fibrinous iritis surprisingly often have a raised E S R (84 per cent against 52 per cent in subacute iritis)

The *antistreptococcal reactions* (A S T and A S H) were doubtfully raised in the uveitis series compared with the normal The difference was not statistically significant

A positive A S T or A S H gives no information of aetiological prognostic or therapeutic value

The *toxoplasmosis tests* (dye test and complement fixation test) should be made in cases of congenital uveitis in infants and older children to disclose toxoplasmic uveitis if present

In adults on the other hand the toxoplasmosis tests give no information of practical value because the reactions most often indicate a previous or present asymptomatic toxoplasmosis with no ocular manifestations

Venereal diseases were responsible for the uveitis in no more than few per cent of the total series Seroreactions and the past history can render likely the diagnoses of syphilitic and gonorrhoeal uveitis

A *raised erythrocyte sedimentation rate* forebodes severer uveitis with increased visual impairment at the culmination of the disease an increased chance of recurrence and a risk of bilateral occurrence

A raised E S R was found in half of the total series and *anaemia* in one third Anaemia and/or a raised E S R occurred in two thirds

General diseases were present in 37 per cent of the uveitis series

An eye with uveitis is a diseased eye in a diseased body *(Oksala)* In many instances it is impossible to diagnose the concurrent general disease but its existence can be suspected through a raised E S R and anaemia

The *S A T-reaction* is rarely positive a fact which argues against frequent presence of chronic rheumatoid arthritis

Examination of patients with uveitis for general diseases would probably be of great value e g examinations for virus diseases of the prostate and seminal vesicle intestinal bacteria with exotoxin production fungus induced diseases worm infestation (Toxocara perhaps Trichocephalus dispar Oxyuris) auto immune reaction to uveal and other tissue etc

If *routine blood tests* are desired in cases of uveitis it seems reasonable at present to choose the following W R G R E S R and in infants and children also the toxoplasmosis test

Other examinations should be made on special suspicion (cf *Hogan Vesterdal)*

Summary

Among 320 patients with uveitis signs of a syphilitic aetiology were noticed in about 1 per cent and a gonorrhoeal aetiology in about 3 per cent The G R was however often negative at the time of occurrence of uveitis

The erythrocyte sedimentation rate was raised in half of the uveitis cases most frequently among those of acute fibrinous iritis and most rarely among those of choroiditis

A raised E S R forebodes an increasing visual impairment during the course of the uveitis an increased chance of recurrence and of bilateral occurrence compared with the cases having a normal sedimentation rate

The streptococcus agglutination test was rarely positive in the uveitis cases (5 per cent)

One third of all the patients with uveitis had anaemia This was present in as much as 44 per cent of those with acute and subacute iritis against only in 19 per cent of those with choroiditis

A raised E S R and/or anaemia was found in two thirds of all the uveitis cases This may *perhaps* be taken as a sign of a concurrent general disease which however rarely is diagnosed

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DESICCATION OF THE PRECORNEAL FILM

I Corneal Wetting Time

BY

M S NORN

The cornea is covered by a thin liquid film called the precorneal film.

This film plays an important part in the nutrition lubrication and coating of the cornea

A *Ehlers* regards the precorneal film as a layer of fluid enclosed in a thin lipoid layer separating the former superficially from the air and on the inside from the corneal epithelium *(Ehlers 1965* A)

The precorneal film is kept distended between the palpebral borders which act as a frame for the film

The film thus covers not only the exposed part of the cornea but also the exposed part of the bulbar conjunctiva It would therefore be most correct to call it the pre ocular film

The remaining part of the conjunctival sac, the retropalpebral space is covered by an epithelium whose surface is marked by mucus and not by lipoid

The precorneal film is the thickest immediately after blinking *Ehlers* in five subjects noticed an average thickness of 8 7 μ 0 2 seconds after blinking The thickness was gradually reduced to on an average 4.5 μ 30 seconds after blinking The reduction took place at the fastest rate in the beg nn ng

If the subject is called upon to avoid blinking a hole will gradually occur in the precorneal film This phenomenon has been observed in both normal and pathological cases

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Rece ved October 5th 1968

The phenomenon was described by *Decker* in 1876 (quoted by *Marx)* and *F Fuchs* in 1911 and others (quoted by *Rollet)*

The interval from the termination of blinking to the occurrence of the defect in the precorneal film has been measured *(Marx Hærn & Marx Rollet)* and the significance of a pathologically *reduced stability of the precorneal film a reduced* wetting time has been discussed

In some pathological cases a corneal area may be seen to remain uncovered *by precorneal film while the eye is open Such desiccated areas may theoretic*ally be regarded as having a wetting time of zero They must be supposed to be moistened when the eye is closed being then covered by conjunctival fluid *and to dry up immediately the eye is opened*

The precorneal film is formed on opening of the eye when the lacrimal streak along the palpebral border becomes partially distended over the cornea *The areas concerned will then at* once *repel the lacrimal fluid and dry up*

No sharp distinction is made in the literature between these two phenomena the local discontinuity with dryness the moment the eye is opened and a hole occurring in the precorneal *film after the eye has* been kept open *for some* time

The present paper deals with the latter phenomenon studied on the basis of a clinical material The permanently dry areas *will be dealt* with in a *future* paper

Different terms are used for the phenomena in the literature dessèchement drying up of the precorneal film discontinuity of the *precorneal film Dellen* indicating the hole in the precorneal film

The *wetting time* in the sense employed in this paper is the interval between the termination of blinking and the occurrence of *interrupted continuity* a hole of the precorneal film

Present Investigations

The series investigated comprised a total of 202 patients from the Ophthalmic Clinic *Kommunehospitalet* and the author s own ophthalmic practice

The corneal wetting time is described in previous papers to have been studied under a magnifier (+ 20 D) by moving a lamp in front of the eye and observing the reflection of the light in the cornea gradually as it reaches the *different* corneal areas After a certain time formation of cavities in the precorneal film have been observed *(Marx Hærn)*

The examiner should aid the patient keeping the eyes open with two fingers *(Hærn)*

Hole formation in the precorneal film is difficult to recognize by this technique or in the slit lamp until the hole has reached a rather considerable extent

In the present study the precorneal film was observed through a Haag Streit slit lamp no 900 To render the precorneal film visible and thus ensure prompt recognition of holes in the film this was vital stained with fluorescein in some cases with novesin (Wander oxibuprocaini chlor) or rose bengal added

One of the following three dye solutions was used

1) 0 125 % fluorescein with sodium chloride added to isotonia without preservative (pH measured at 4 26 at the Central Laboratory *Kommunehospitalet)*

2) fluorescein novesin mixture acc to *Fenton* containing 0 125 % fluorescein 0 3 % novesin and 0 0025 % phenylmercuric nitrate as preservative as well as sodium chloride added to isotonia (pH 6 65 6 37)

3) fluorescein rose bengal mixture 50 mg fluorescein sodium 50 mg rose bengal 45 mg sodium chloride distilled water to 5 g with 0 001 % phenyl mercuric nitrate added (pH 7 70)

The dye solution was instilled into the inferior conjunctival fornix from a neddle mounted tube (*Norn* 1967) delivering a drop of 0 01 ml Blinking caused the dye solution to mix with conjunctival fluid which likewise constitutes about 0 01 ml (Norn 1966) By this procedure the precorneal film and the lacrimal streak also became stained

After having now been placed in front of the slit lamp the patient was instructed to blink a few times and then keep the eyes open looking straight forwards

A stop watch was started immediately after the last blink The precorneal film was observed in cobalt filtered blue light through a 1 2 mm broad vertical slit in a dimly lit room

The slit was moved regularly from side to side across the cornea until a hole formation was detected in the fluorescein stained precorneal film At this moment the stop watch was stopped

The beam of light entered obliquely to secure the best possible observation of the precorneal film

The reading may in some instances take place with a minor delay because the slit has not yet reached the site of the hole formation at the moment this is started

The fairly narrow slit was nevertheless chosen because the precorneal film is more difficult to study with a broader slit

The patient s lid was never supported as this would constitute an important source of error The framing effect of the lids might be interfered with and thus reduce the wetting time of the precorneal film

Relatively few patients were unable to keep their eyes open for a sufficiently long time The test never failed using a novesin fluorescein mixture

The hole formation manifested itself as a black area in the fluorescent yel

lowish green precorneal film The hole was round oval or streak shaped and increased rapidly in size Sometimes new holes or streaks were formed close by or elsewhere soon making the precorneal film be crossed by a network of holes and streaks

These holes and streaks disappeared immediately on blinking which effected reproduction of the normal precorneal film

The test was interrupted after started hole formation and repeated altogether three times If the colour of the *precorneal film had faded* instillation of dye solution was repeated before the next test

The bulbar conjunctiva was seen not to be covered by a regular film but *fluorescein gathered in* grooves between the numerous fine conjunctival folds

Test Errors

Defects of the *precorneal film* are recognizable very soon after instillation of a dye solution On the other hand addition of a dye may be conceived to alter the properties of the precorneal film

The results of the different staining methods used in the normal series are shown in table I There *seemed to be no difference* between a *0 125 % isotonic* fluorescein solution and a corresponding solution with novesin and a preservative added

Novesin and a preservative thus apparently did not alter the stability of the precorneal film

A mixture of rose bengal and fluorescein (1 % of each) on the other hand seemed to reduce the wetting time thus suggesting that the higher dye concentration had an unfavourable *influence on the stability of the film* The material is however too small to allow of any definite conclusions

The weak fluorescein solution possibly in itself alters the wetting time but *the alteration is then uniform throughout* Rose bengal was used in no more than 34 out of 160 patients

The properties of the precorneal film might be conceived to alter in the

Table I

Wetting time in normal series studied by different staining techniques

Stain technique	pure fluorescein (0 125 %)	novesin fluorescein	rose bengal fluorescein
Number of tests	65	103	15
Aver wetting time	*26 0*	*28 0*	*21 9*

course of the first test so that accordingly the next two tests might give in correct values

The results of the first second and third tests on the normal subjects are recorded in table II

The wetting time was perhaps, a little shorter on the second and third tests than on the first but the difference is not significant

Normal Material

Site

The wetting time was read during three tests on each of 64 normal eyes

In 124 cases the site of the hole in the precorneal film was set out in a diagram In 40 cases the first hole occurred temporally on the cornea and in 43 nasally In 41 cases the hole occurred in the vertical mid zone of the cornea so close to the midline that it could be classified neither as definitely nasal nor as definitely temporal

The site of the hole often changed from test to test on the same eye Thus for instance the hole might occur temporally on the first test nasally on the second and mesially on the third In no more than 15 per cent was the hole found at the same site or nearly so on the three tests

Marx stated that dessication of the precorneal film most often occurs temporally This view could not be borne out througt the present studies which seemed to show no rules for the site

Humidity

The humidity of the conculting room in which the wetting time was determined varied from 40 to 65 % measured with hair hygrometer Within this range no unquestionable correlation was found between humidity and wetting time The

Table II

Wetting time in normal series Results of first second and third readings

	first reading	second reading	third reading
Number of tests	64	6[illegible]	59
Average wetting time	30 0	[illegible] 5	25 1

wetting time was 27 seconds at humidity 40 49 % 50 54 % and 55 59 % and 28 seconds at 60 64 %

A possible evaporation thus seems to have no particular influence on the wetting time within the range of normal humidity in a consulting room

Temperature

The room temperatures at reading of the wetting time ranged from 18 to 24° C No correlation was noticed between room temperature and wetting time

Width of Palpebral Fissure

The width of the palpebral fissure was measured with a measuring ocular under the same conditions as employed for the wetting time test A relatively narrow palpebral fissure might be conceived to give a more stable precorneal film than a wide one the film being distended over a fairly small area A wide fissure might cause a shorter wetting time

Table III shows however that there was no correlation between width of palpebral fissure and wetting time

Foam

Larger or smaller quantities of foam were found at the outer canthus along the palpebral border and more rarely at the inner canthus

Foam formation depends on the physical properties of the conjunctival fluid It increases in response to rising viscosity and rising surface activity The amount of foam is augmented by frequent blinking (*Norn* 1963 B)

The amounts of foam were roughly graded 1 to 5 3 indicating a moderate amount 4 a slightly increased and 2 a slightly reduced amount while 1 and 5 represent the extreme values minimum and maximum respectively

Table IV shows that no definite correlation was demonstrable between quantity of foam and wetting time

Table III

Width of palpebral fissure and wetting time (Normal series)

Palpebr fissure (mm)	6–7	8	9	10	11	12	13	14
number of tests	15	6	47	27	21	24	6	7
aver wetting time (seconds)	24	37	24	29	24	30	36	34

Table IV

Foam formation at outer canthus and along palpebral border compared with wetting time in normal series

Foam amount (arbitrary grading)	1	2	3	4	5
Number of tests	53	71	25	24	5
aver. wetting time (seconds)	25	31	27	26	33

Intra Ocular Tension

In 7? cases the intra ocular tension was measured with Goldmann's applanation tonometer and compared with the wetting time which had been measured previously.

No correlation was demonstrable between the tension and the corneal wetting time within the observed range of tensions 8–19 mm.

Normal Value

The mean wetting time was 26.8 seconds in normals when all the tests were included, i. e. three tests on each subject.

By reckoning only the *first* test on each subject a normal mean value of 30.0 seconds was attained to.

The shortest wetting time recorded for a normal was 3 seconds and the longest 13? seconds. Great variations were in some cases noticed in the individual subject.

The distribution of the values seen in the normal series is shown in table V partly those obtained by the first test and partly the mean values of all three tests.

The values were generally lower than those in *Hæn & Marx* series from 19?6, in which the mean wetting time was 6? seconds with minimum 5 and

Table V

Distribution of the wetting time values over the total normal series (184 tests)

Wetting time in seconds	3–9	10–19	20–29	30–?9	40–49	50–59	≥ 60
Percentage distribution	1	[illegible]	17	[illegible]	5	4	8

wetting time was 27 seconds at humidity 40 49 % 50 54 % and 55 59 % and 28 seconds at 60 64 %

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number of tests	15	6	47	27	21	24	6	7
aver wetting time (seconds)	24	37	24	29	24	30	36	34

males against in 47 per cent of the males The difference is significant ($t = 3.1$ $0.01 > P > 0.001$)

This observation was unexpected *Hæn & Marx* found no significant sex difference or age variation

It is difficult to explain why the female precorneal film generally bursts sooner than the male

The tear secretion is approximately the same for the two sexes (Norn 1965) Further the average amount of conjunctival mucus (*Norn* 1963 A) and the flow of the mucous thread in the inferior conjunctival fornix (*Norn* 1969 A) seem to be equal

The two sexes show no difference with regard to frequency of blinking (Cf a report on the blinking frequency of 50 patients examined in slit lamp without having been informed in advance on the object of this examination (table VII))

The corneal light reflex is reduced in pregnant women but beyond this no sex difference has been found with regard to the photo electrically measured light reflex (*J Edmund*)

However the precorneal film of women also differs beyond the fertile age from that of men (table VI)

Pathological Material

A series of 96 patients was subjected to 288 tests The diagnoses are shown in *table VIII* Miscellaneous comprises few cases of blepharitis meibomitis epiphora exophthalmos glaucoma iritis facial palsy dacryoadenitis

A mean wetting time of 2?.3 seconds was calculated for the pathological material a little shorter than that for the normal 26 8 seconds The difference between the two sexes was smaller than in the normal material (females 21 4 and males ?4 0 seconds)

A reduced wetting time was found in mild cases of *marginal keratitis* while permanently dry areas were seen in severer cases the wetting time being zero Cases with wetting time zero was excluded from this series see *Norn* 1969 B)

The wetting time was normal in cases of inactive corneal defects (healed up

Table VII

Length of blinking interval in 31 females and 19 males

Blinking interval (seconds)	5–6	7–8	≥9
Percentage of females	*61*	*6?*	64

maximum 235 seconds In 54 per cent the time value exceeded 55 seconds while in the present series only 21 per cent presented values above 50 seconds at the first test

Age

The wetting time seemed to be independent of age for persons between the ages of 10 and 70 (table VI)

No child under 10 was tested, because the test requires that the subject keeps quiet

In patients over 70 the wetting time seemed to become reduced with increasing age The stated age distribution was also found at the first second and third tests separately and within either sex

Sex

The wetting time was found to be shorter in females than in males

The first test gave a mean wetting time in seconds for women of 24 4 ± 3 9 and for men 36 4 ± 4 2

In the total material the females were found to have a mean wetting time of 23 0 ± 1 9 and males 31 6 ± 2 0

A wetting time exceeding 30 seconds was noticed in 25 per cent of the fe

Table VI

Wetting time in normal series Age and sex distribution (First reading first four columns Total series (three readings per subject last two columns)

Age	females		males		total series	
	number	wetting time	number	wetting time	number	wetting time
10–19	0	0	2	46	4	36
20–29	4	27	3	60	21	39
30–39	2	15	1	66	9	24
40–49	1	13[illegible]	4	30	15	35
50–59	15	23	9	28	[illegible]	[illegible]5
60–69	6	21	6	41	39	2[illegible]
70–79	2	14	3	25	13	20
80–89	2	8	2	30	1[illegible]	16
Total	34	24 4	30	36 4	184	[illegible]

ral years after the active process an average wetting time of 23 seconds was found Most of these patients had a considerably reduced corneal sensitivity

Thus Marx statement that desiccation of the cornea is accelerated by a reduced corneal sensitivity was not borne out

Hœn & Marx found a reduced wetting time in cases of diplobacillary conjunctivitis and conjunctival scrophula These diseases were not represented in the series under review

Hœn found a reduced wetting time in episcleritis The small number of cases in the present series showed the same tendency

Pathological cases displaying prolonged wetting time were not demonstated to exist

Vital Staining

The cornea became vital stained in 40 cases (35 corneae were stained by fluorescein and [illegible]0 by rose bengal) The vital stained areas did not *constitute* the points of origin of hole formation in the precorneal film

Fluorescein staining disclose lesions of the *corneal epithelium while rose* bengal stains degenerate cells in the surface epithelium of the cornea (Norn 1964)

Thus neither epithelial lesions nor areas with degenerate cells have any influence on the location of the holes *occurring* in the precorneal film after a certain period of exposure

The site of the hole bears no relation to the location of corneal opacity nor to *Hudson Stahli*s pigment line on the cornea

The cornea stained by *rose bengal tended* to have a short wetting time (Cf the short wetting time in keratoconjunctivitis sicca) The fluorescein stainable *corneae* on the other hand had the same wetting time as the non stained (Table IX)

Table IX

Wetting time studies in cases with vital staining of the cornea a total of 40 cases

Vital staining	number of eyes	wetting time first test	wetting time all three tests
Fluorescein	5	21	21
Rose bengal	[illegible]0	11	15

Table VIII

Wetting time in the pathological material Each patient was subjected to three tests A total of 288 tests

Diagnosis	numb of pts	first test wetting time	mean of all tests wetting time
seq of corneal erosion	6	17	18
mild marginal keratitis	3	6	6
seq of corneal corrosion	3	18	24
seq of foreign body in cornea	4	18	18
corneal opacity	9	39	24
contact lens wearers	5	15	18
keratoconjunctivitis sicca	4	6	5
allergic conjunctivitis	4	26	38
acute infect conjunctivitis	6	31	25
chronic infect conjunctivitis	6	13	17
chron simple conjunctivitis	8	29	34
catar extr few days before	5	12	14
trichiasis	3	13	15
episcleritis	4	6	11
Miscellaneous	26	25	24
Total	96	21	[illegible]
normal series	64	30	[illegible]

corneal erosion sequelae of foreign bodies and slaked lime corrosion corneal opacity wearing of contact lenses) Active corneal diseases on the other hand caused permanently dry areas (foreign bodies keratitis granular cornea See *Norn* 1969 B)

The wetting time was found to be reduced in keratoconjunctivitis sicca both on tests with pure fluorescein (three cases) and tests with a fluorescein – rose bengal mixture (5 seconds)

The other conjunctival diseases such as infectious and allergic conjunctivitis seemed not to interfere with the wetting time

In simple chronic conjunctivitis the continual conjunctival complaints despite absent objective findings might be due to deficient lubrication between the cornea and conjunctiva This theory was not supported however by the results of the present investigation the wetting time being not reduced

A *reduced corneal sensitivity* seemed to have no influence on the wetting time In a preliminary series of 29 cases of dendritic keratitis followed up seve

with Sudan stained lipid phase in white light disclosed however that the holes were drops of fat replacing the normal precorneal film Proper holes were not detected in the mottled picture and the wetting time in a fat containing precorneal film could not be determined by this technique

Ophtasiloxan (Laboratoire P O S Kayserberg France) is a viscous liquid consisting of silicone containing polyethylene glycol used for draining of corneal oedema

After instillation of ophtasiloxan holes were seen all over the precorneal film These holes consisted of the polyethylene glycol phase which was thinner than the surrounding normal precorneal film and which presumably was responsible for the corneal dehydration

Mechanical Influence

By withdrawing the subject s lids so much that the palpebral borders lost contact with the cornea and conjunctiva the wetting time was found to decrease appreciably from on an average 37 to 7 seconds (seven experiments)

This indicated that the palpebral border represents a framing effect of decisive importance with regard to the stability of the precorneal film as shown by *Ehlers* (1965 A)

Use of a corneal sensimeter gave rise to very fine fluorescein stained corneal lesions at the site where the nylon thread was pressed against the cornea

These lesions were not followed by holes in the precorneal film not even in the cases where maximum force (shortest thread length) was employed (1 t8 g mm² nylon thread thickness 0 12 mm Cochet & Bonnets sensimeter)

Greater lesions on the other hand (e g due to removal of foreign bodies with a bud shaped bur) were seen to leave permanent holes in the precorneal film

Tonometry caused flattening of the cornea and rose bengal stainable areas might be seen The wetting time seemed to be normal however following applanation and precorneal holes occurred irregularly within and outside the corneal area exposed to applanation

Discussion

The method described above for studying the stability of the precorneal film is subject to the possible source of error that a dyestuff is added to the film whose properties it is desired to investigate

The precorneal film is diluted with an aqueous fluorescein solution instilled in a volume of 0 01 ml into the conjunctival sac which itself contains about

The cornea may be affected within the area in which the hole is formed in the precorneal film In the present study the patient was made to blink immediately after the first hole in the film had been recorded The next test showed no vital staining of the previously hole containing area

By leaving the patient with open eyes for 10 to 20 seconds after started hole formation subsequent vital staining would in some cases give a very fine fluorescein staining over larger or smaller proportions of the original hole area No simultaneous rose bengal staining was seen after this short term desiccation

Experimental Studies

A total of 22 subjects were subjected to experimental studies

Anaesthetics

Instillation of cocaine into the conjunctival sac reduced the wetting time

Cocaine in concentrations of 2 % and 4 % had a weak effect while painting of the inferior conjunctival fornix with 10 % cocaine reduced the wetting time to zero The precorneal film cracked immediately

The cocaine effect on the precorneal film has been conceived to bear relation to its cornea anaesthetic action (*Hærn Rollet*)

However experiments with 0 3 % novesin (table I) and instillation of a 1 % solution showed that a totally effective anaesthesia of the cornea does not influence the wetting time

Thus the cocaine induced reduction of the wetting time was not due to its anaesthetic action

N Ehlers (1965 B) has demonstrated by electron microscopy that cocaine destroys the superficial cells of the corneal epithelium thereby presumably damaging the basis of the precorneal film

Precorneal Film Substitute

Methocel (0 5 %methylcellulose) prolonged the wetting time The precorneal film seemed to grow thicker and the wetting time was prolonged on an average from 5 to 42 seconds

1 4 %polyvinyl alcohol caused only a doubtful prolongation of the wetting time

Ointment (vaseline) and oil (arachis oil) may alter the appearance of the precorneal film By the technique employed in the present study large holes were seen scattered over the fluorescein stained precorneal film Examination

factors as degeneration of the corneal epithelium minor epithelial lesions corneal opacity Hudson Stahli s line and flattening of the cornea during applanation tonometry

The fact that the wetting time was found to be reduced after instillation of cocaine and in cases of mild marginal keratitis argues in favour of a certain importance of the corneal condition

An altered viscosity of the precorneal film (addition of methylcellulose) may change the wetting time Similarly the reduced wetting time in keratoconjunctivitis sicca may be due to an altered composition of the precorneal film (reduced amount of lacrimal fluid increased content of mucus)

Thus no local process in the cornea interferes with the wetting time but this depends on extensive alterations of the corneal surface and of the composition of the precorneal film

Measurement of the wetting time seems to be of no clinical interest in practice It is true that a greatly reduced wetting time raises suspicion of a pathological process (keratoconjunctivitis sicca marginal keratitis) but on the other hand the normal range of variations is so great that such a short wetting time as 3 seconds was recorded in the normal series

Recording of permanent holes i e holes in the precorneal film present on opening of the eye after blinking is of practical importance this phenomenon being pathological having never been noticed in any normal subject and being always localized at the site of the pathological process (wetting time zero)

This phenomenon will be described in a future paper (*Norn* 1969 B)

Summary

A total of 202 subjects were examined with a view to studying *how long* the fluorescein stained precorneal film is intact from the termination of blinking to the occurrence of holes in the film (wetting time)

In normals the wetting time averaged 30 seconds though with a wide range of variations (3 132 *seconds*)

The wetting time was found to be *shorter in females* than in males to decrease after the age of 40 to be prolonged by adding methylcellulose and be reduced by *instilling cocaine or by* withdrawing the lids from the cornea Further it was seen to be reduced in cases *of* keratoconjunctivitis sicca and marginal keratitis

The wetting time seemed to be *independent* of foam formation at the inner canthus and of the width of *the palpebral fissure*

The holes occurred at irregular sites *being independent* of possibly existing corneal opacity epithelial degeneration or *minor corneal* lesions

0 01 ml of fluid The precorneal film thus becomes mixed with an equal part of dye solution

However most of the tests were made with a weak fluorescein solution (0 125 %) which is isotonic and has a pH value close to that of the lacrimal fluid

Fluorescein possibly reduces the wetting time of the precorneal film *Hæn & Marx* found a longer average wetting time in the cases where they studied the untreated film than in those where a dye had been added

On the other hand a beginning hole formation is difficult to detect in an unstained precorneal film Hæn s high figures may be due to the hole formation being not detected till at a fairly advanced stage by his technique

The wetting time results vary within a considerable range in part also in the individual subject The series investigated was however sufficiently large to demonstrate that the wetting time is *shorter for females than for males*

Hæn & Marx found no sex or age difference in their series

The wetting time seemed to decrease with increasing age though not till after the age of 70 The age curve therefore does not correspond to that for the tear secretion which falls from the age of about 30 (*Norn* 1965)

Rollet entertained the idea that the hole formation in the precorneal film has an influence on the *blinking reflex* According to his theory the holes be come repaired by a blinking reflex released *via* the 5th and 7th cranial nerves

A blinking interval lasts about 5 10 seconds The present investigation showed the wetting time of normals to average about 30 seconds with a wide range of variations (3 132 seconds)

This means that holes usually are not formed under physiological conditions

In most cases it was easy to make the subjects keep their eyes open and thus intentionally suppress the blinking reflex throughout the test period also beyond the time of occurrence of the first hole

This could even be carried through in cases of non anaesthetized eyes sug gesting that the hole formation in the precorneal film has no influence on the blinking reflex

The blinking reflex is presumably controlled from a blinking centre be ng relatively independent of extrinsic stimuli *(Davson)*

Which factors determine the stability of the precorneal film?

Does the wetting time depend on the composition of the precorneal film or on the state of its foundation i e the cornea?

If the stability of the film depends on local factors in the cornea we should expect the hole formation to occur in the same corneal area at repeated tests on the same subject This is not so however On the contrary the holes were seen to be formed at different sites and to be completely independent of such local

factors as degeneration of the corneal epithelium minor epithelial lesions corneal opacity Hudson Stahli s line and flattening of the cornea during applanation tonometry

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Summary

A total of 207 subjects were examined with a view to studying how long the fluorescein stained precorneal film is intact from the termination of blinking to the occurrence of holes *in the film (wetting* time)

In normals the wetting time averaged 30 seconds, though with a wide range of variations (3 132 seconds)

The wetting time was found to be shorter in females than in males to decrease after the age of 70 to be prolonged by adding methylcellulose and be reduced by instilling cocaine or by *withdrawing the lids* from the cornea Further it was seen to be reduced in cases of keratoconjunctivitis sicca and marginal keratitis

The wetting time seemed to be independent of foam formation at the inner canthus and of the width of the palpebral fissure

The holes occurred at irregular sites being independent of possibly existing corneal opacity epithelial degeneration or minor corneal lesions

0.01 ml of fluid. The precorneal film thus becomes mixed with an equal part of dye solution.

However, most of the tests were made with a weak fluorescein solution (0.125 %), which is isotonic and has a pH value close to that of the lacrimal fluid.

Fluorescein possibly reduces the wetting time of the precorneal film. *Hæn* & *Marx* found a longer average wetting time in the cases where they studied the untreated film than in those where a dye had been added.

On the other hand, a beginning hole formation is difficult to detect in an unstained precorneal film. Hæn's high figures may be due to the hole formation being not detected till at a fairly advanced stage by his technique.

The wetting time results vary within a considerable range, in part also in the individual subject. The series investigated was however sufficiently large to demonstrate that the wetting time is *shorter for females than for males*.

Hæn & *Marx* found no sex or age difference in their series.

The wetting time seemed to decrease with increasing age, though not till after the age of 70. The age curve therefore does not correspond to that for the tear secretion which falls from the age of about 30 (*Norn* 1965).

Rollet entertained the idea that the hole formation in the precorneal film has an influence on the *blinking reflex*. According to his theory, the holes become repaired by a blinking reflex released *via* the 5th and 7th cranial nerves.

A blinking interval lasts about 5-10 seconds. The present investigation showed the wetting time of normals to average about 30 seconds with a wide range of variations (3-132 seconds).

This means that holes usually are not formed under physiological conditions.

In most cases it was easy to make the subjects keep their eyes open and thus intentionally suppress the blinking reflex throughout the test period also beyond the time of occurrence of the first hole.

This could even be carried through in cases of non-anaesthetized eyes suggesting that the hole formation in the precorneal film has no influence on the blinking reflex.

The blinking reflex is presumably controlled from a blinking centre being relatively independent of extrinsic stimuli (*Davson*).

Which factors determine the stability of the precorneal film?

Does the wetting time depend on the composition of the precorneal film or on the state of its foundation, i.e. the cornea?

If the stability of the film depends on local factors in the cornea, we should expect the hole formation to occur in the same corneal area at repeated tests on the same subject. This is not so, however. On the contrary, the holes were seen to be formed at different sites and to be completely independent of such local

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DESICCATION OF THE PRECORNEAL FILM

II Permanent Discontinuity and Dellen

BY

M S NORN

The thin liquid layer covering the cornea is called the precorneal film This film may be more or less stable It bursts at a shorter or longer *interval after blinking* to be regenerated after another blink when fresh fluid from the lacrimal streaks along the palpebral borders spread over the cornea

In some instances however permanent holes are *present in the precorneal film* The underlying corneal areas are always dry These areas are presumably moistened by conjunctival fluid when covered by the palpebral conjunctiva on blinking but they seems dry as soon as the corneal area concerned becomes exposed

The cornea can be excavated at the site of a permanent defect of the pre corneal film Such excavations are *termed* Dellen Dellen have been described before the concept of hole formation in the precorneal film was known

I Fuchs described Dellen in 1911 (quoted by *Baum*) in relation to episcleritis scleritis thick pinguecula lagophthalmos after *instillation* of cocaine as a sequela of ocular muscle *operation* following cataract extraction and occurring spontaneously in elderly persons

Barraquer has also seen Dellen in cases of keratoprosthesis

Baum et al added to these Dellen in cases of pterygium limbus bordering dermoids limbus *bordering conjunctival* carcinomas and subconjunctival haemorrhage

Vascular and neurotrophic disorders have been suggested as causes of Dellen

Received October th 1968

In 42 cases a permanent hole was found in the precorneal film The wetting time was zero This phenomenon is pathological and must be distinguished from that described above where there is a certain interval between the termination of blinking and the occurrence of a hole formation

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Table I

Permanent hole formation in the precorneal film

Diagnoses for a total of 42 patients with wetting time zero among 202 examined

Diagnosis	number of patients
pterygium	2
marginal keratitis pronounced	2
foreign body in cornea	4
corneal erosion with vital staining	7
dentritic keratitis	9
transplantation of cornea	5
granular cornea	11
lagophthalmos	1
cocaine 10%	1
Total	42

was only found in association with corneal lesions in the widest sense *including* pterygium for instance. A permanent hole was seen in 59 per cent of the eyes with corneal lesions.

All the 42 cases with a dry area in the precorneal film have been *set out in* table I.

No cases of unquestionable Dellen were *recorded*.

In the four eyes affected with *pterygium* the desiccated area was seen as a *broad crescent* on the cornea encircling the invasive pterygium base.

The dry areas were thus found at the angle between the *projecting* conjunctival epithelium on the pterygium and the corneal *epithelium at the shifting* of level.

The film covering the *cornea* was otherwise smooth while that *covering* the pterygium formed longitudinal grooves between the conjunctival folds of the pterygium.

In cases of *marginal keratitis a crescent or round* hole was seen round the vital stained process. The precorneal *film* was found to be more stable in relation to a not *particularly* pronounced marginal *keratitis* but *still the hole* formation occurred sooner than in normal eyes (*Norn* 1969).

Foreign bodies on the cornea were surrounded by a ring with absent precorneal film. The film was thus absent not only at the site of the foreign body but also over an area several times the size of the foreign body.

In one case in which the foreign body *had been removed* a small vesicle had formed. The area corresponding to this vesicle was permanently dry.

Baum et al and *Barraquer* pointed to the precorneal film as the primary cause Elevation of the cornea or conjunctiva effects a discontinuity of the fat containing precorneal film This interrupted continuity gives occasion to local evaporation resulting in reduction of the water content of the conjunctival stroma at the site concerned with a consequent excavation The connective tissue fibrils are present in normal numbers but compressed The epithelium may be intact or injured

According to *Baum* the treatment of Dellen must consist in prevention of evaporation (dressing ointment polyvinyl alcohol) and lowering of a paralimbal elevation (steroids and possibly antibiotics against inflammation)

Presence of Dellen has most often been described in the limbal region Permanently dry areas of the precorneal film may however also be found in the more central regions of the cornea

The object of the present investigation was to study the occurrence of such permanently dry areas of the precorneal film with or without associated excavation of the cornea itself

Present Investigations

Procedure

The precorneal film was rendered visible by vital staining with 0 125 % fluorescein more rarely with a mixture of 1 % fluorescein and 1 % rose bengal It may be difficult to see holes in the precorneal film especially small holes without previous vital staining

The precorneal film was examined in a Haag Streit slit lamp no 900 with cobalt filtered light entering obliquely through a 1 2 mm broad slit The method has been described by *Norn* (1969)

Material

A total of 202 corneae from 202 subjects were examined 64 of these cases were normal and 138 pathological Of the latter 71 had corneal lesions

Thus a special interest was taken in cornea diseases while conjunctival and other diseases constituted a considerably smaller proportion

Result

A permanently dry area of the precorneal film was noticed in 42 of the 202 cases (21 per cent)

A permanently dry hole has never been demonstrated in the precorneal film of normals where holes do not occur till on an average 30 seconds after blinking The shortest interval recorded was 3 seconds *(Norn* 1969)

In the present series a permanently desiccated area of the precorneal film

Touching of the inferior conjunctival fornix by a swab moistened with 10 % cocaine resulted in immediate occurrence of large holes all over the precorneal film scattered between and round fluorescein stained areas

All the subjects had this test repeated three times They all presented permanent holes at the same site each time as a result of a pathological process localized in the cornea (erosion keratitis foreign body vesicle)

The hole might be located over a vital stained area (erosion) or be totally independent of vital stainable regions (vesicle)

Discussion

The present investigation showed that the permanently dry hole in the precorneal film may be localized anywhere on the cornea and not particularly in the limbal region as the literature might suggest

The hole formation in the precorneal film over a vesicle on the cornea may have the following cause

The vesicle is due for instance to a raised intrabulbar pressure The localized swelling is accountable for by oedema of the cells of the corneal epithelium The vesicle projects into the precorneal film similarly as a rock towers above the sea level The precorneal film might be conceived to continue as a layer across the vesicle but evidently the surface active forces are incapable of effecting a coating of the projecting process

Ehlers has shown that the precorneal film may be regarded as a fluid enveloped in a thin layer of lipid Apparently the top of the vesicle loses the required lipid layer which must be supposed to continue from the surface of the normal corneal epithelium along the base of the vesicle thereafter to turn over and continue on the surface of the precorneal film thus forming a layer between this and the atmosphere

The conditions are more difficult to analyze in cases of erosion The hole formation in the precorneal film definitely extends beyond the eroded area on to apparently normal corneal epithelium The erosion might be conceived to be surrounded by a ped of oedema causing hole formations in the same manner as vesicles The hole formation may then be compared to a coral island Crescent holes round the erosion justify the comparison It cannot be settled whether the excavated erosion itself is covered by precorneal film or whether it is dry and is included in the hole formation in the precorneal film

Wepppard et al on histological examination of rabbits with congenital glaucoma noticed that erosions may be covered by a precorneal like film, stained by haematoxylin eosin and Papanicolaou s stain The possibility that the film

Corneal erosions of a certain size were surrounded by a ring with absent pre corneal film Lesions 0 12 mm in diameter or smaller such as are provoked by a corneal sensimeter caused no hole formation in the precorneal film (*Norn* 1969)

Larger erosions were seen to be surrounded by a dry ring extending far beyond the eroded area The erosion itself was stained intensely by the instilled fluorescein the dye having penetrated into the parenchyma through the epi thelial defect Round this there was found an unstained ring which again was surrounded by a normally stained precorneal film

It is difficult to decide whether the erosion itself was covered by precorneal film or whether the precorneal film was absent both over the erosion itself and over a broad space round this

In one case of a two days old erosion the eroded area remained unstained and the entire formed a circular dry spot After repeated dyeing a weak fluorescein staining was seen centrally in the erosion indicating that a small epithelial defect was still left This case suggests that both the erosion itself and its surroundings lack precorneal film

The method is thus a very sensitive one for disclosing residual erosion

Dendritic keratitis at the active stage when vital stained displayed perma nent hole formation at the site of the active process (three cases)

In four cases of parenchymatous metaherpetic keratitis with vesicles holes were found over these In some cases of corneal opacity after dendritic kera titis permanent holes were seen round a rose bengal stained area Corneal opacity with no vital staining or vesicles left no permanent holes in the pre corneal film

After *corneal transplantation* permanent hole formations were noticed in the precorneal film over vesicles even over very small ones and occasionally also round places where there have been sutures where it might be difficult to decide whether fine vesicles were present The method is suitable for detecting even very small vesicles and other differences in level which ordinary slit lamp examination may fail to disclose

In the cases of *granular cornea* a large number of holes were seen over the vesicles formed The great majority of these were scattered small holes but a few bigger ones were also often noticed at the sites of larger vesicles These holes in the precorneal film were independent of a possible concurrent vital staining

The eleven granular corneae were found in relation to the following dis eases glaucoma endophthalmia zoster bandular cornea degeneration sequelae of cataract extraction Fuchs dystrophy and Groenow s corneal dystrophy

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The hole formation in the precorneal film over a vesicle on the cornea may have the following cause

The vesicle is due for instance to a raised intrabulbar pressure The localized swelling is accountable for by oedema of the cells of the corneal epithelium The vesicle projects into the precorneal film similarly as a rock towers above the sea level The precorneal film might be conceived to continue as a layer across the vesicle but evidently the surface active forces are incapable of ef fecting a coating of the projecting process

N Ehlers has shown that the precorneal film may be regarded as a fluid en veloped in a thin layer of lipid Apparently the top of the vesicle loses the re quired lipid layer which must be supposed to continue from the surface of the normal corneal epithelium along the base of the vesicle thereafter to turn over and continue on the surface of the precorneal film thus forming a layer be tween this and the atmosphere

The conditions are more difficult to analyze in cases of erosion The hole formation in the precorneal film definitely extends beyond the eroded area on to apparently normal corneal epithelium The erosion might be conceived to be surrounded by a ped of oedema causing hole formations in the same manner as vesicles The hole formation may then be compared to a coral island Crescent holes round the erosion justify the comparison It cannot be settled whether the excavated erosion itself is covered by precorneal film or whether it is dry and is included in the hole formation in the precorneal film

Sheppard et al on histological examination of rabbits with congenital glau coma noticed that erosions may be covered by a precorneal like film stained by haematoxylin eosin and Papanicolaou s stain The possibility that the film

consists of serous exudate can hardly be excluded however On slit lamp examination the erosion and its surroundings seem not to be covered by precorneal film

Permanent holes in the precorneal film in the limbal region may be caused by differences of level (pterygium) The hole formation may give occasion to excavation of the cornea itself proper Dellen as described by *Barraquer* and *Baum* Similar excavations *may however occur elsewhere in the cornea* also centrally, presumably likewise preceded by a hole in the precorneal film

The present investigations allowed of no conclusions regarding the bottom of the hole in the precorneal film The bottom may consist of apparently normal corneal epithelial cells which are not vital stained

A thin liquid layer may possibly be found at the bottom of the hole but if so this is at least very much thinner than the normal precorneal film

The epithelial cells within the hole formation probably lack the normal superficial lipid layer

The present study revealed *a difference in principle between permanent hole formation in the precorneal film and that occurring some time after blinking*

The former phenomenon is only met with in pathological cases

It remains at the same site at which a local lesion usually is detectable This latter must be supposed to be responsible for the hole

Holes occurring after a period of exposure have also been seen in normals Their sites change from test to test on the same cornea being independent of possible local processes in this Such holes are of no proper diagnostic importance

It it true that hole formation occurs particularly soon in relation to keratoconjunctivitis sicca but similarly has been noticed in a few normals

Recording of the wetting time (i e the interval from the termination of blinking to occurrence of the first hole) is therefore of no particular clinical *importance*

Recording of a permanently dry hole (wetting time zero) on the other hand *is of practical importance first because this indicates presence* of a pathological process and secondly because it allows the examiner to localize the pathological process on the cornea (e g a residual erosion *that is so slight* that it can be recognized by no other method)

Diagnosis of Superficial Corneal Pathology

We may conclude from the results of the present study that the diagnostic possibilities within the field of superficial corneal pathology can be improved in a few instances *by observing the fluorescein stained* precorneal film

Table II

Diagnostic methods for superficial corneal lesions

method	diagnostic importance	site
permanent discontinuity of the precorneal film (wetting time zero)	vesicle erosion keratitis foreign body etc	defect of superficial lipid layer of cornea
vital staining with fluorescein	lesion (discontinuity) of corneal epithelium	superficial epithelial layer
vital staining with rose bengal	degeneration of corneal epithelial cells	superficial epithelial layer
defect of *Fischer Schweitzer*'s polygonal pattern (anterior corneal mosaic)	lesion or cicatrix	superficial connective tissue or basal epithelial layer

A hole seen in the cobalt filtered light of the slit lamp immediately after blinking indicates that the corneal area concerned is pathological presumably because it is deprived of the corneal lipid film (Vesicle erosion foreign body keratitis etc)

Holes occurring some seconds after exposure are of no clinical interest

Other methods of diagnostic value are those of *vital staining* and *Fischer Schweitzer*'s polygonal pattern

Fluorescein staining discloses lesions (discontinuity) of the corneal epithelium while rose bengal staining shows areas with degenerate epithelial cells Staining with a mixture of 1 % fluorescein and 1 % rose bengal is expedient (*Norn* 1964)

Fischer in 1928 subjected a polygonal pattern on the cornea to reflectographic study In 196 *Schweitzer* showed that such a pattern can be provoked by rubbing the patient's lid after fluorescein staining The phenomenon can be observed direct in the slit lamp

Bron (1968) and *Norn* (1968) demonstrated independently that a corresponding negative pattern may be seen through a glass plate or an applanation prism pressed against the cornea

Fischer Schweitzer's polygonal pattern (anterior corneal mosaic) is provoked in the following manner

After vital staining with fluorescein (1 %) the patient closes the eye and the examiner rubs the upper lid with a finger from side to side or up and down using moderate force The eye is opened immediately after discontinuation of

the massage and the result is promptly observed in the slit lamp in front of which the patient is sitting during the massage

The mosaic pattern can be provoked in almost any case though sometimes not till after repeated rubbing possibly also of the lower lid

A defect of the mosaic pattern is pathological suggesting a lesion or cicatrisation round Bowman's membrane in the basal epithelial layer or in the superficial corneal connective tissue

The diagnostic methods described above can disclose changes in the superficial corneal layer which may not be detected by ordinary slit lamp examination or special slit lamp examination such as retro illumination and scleral scatter

Table II *shows the sites of the changes in the cornea*

Summary

Permanent holes in the fluorescein stained precorneal film were found in 4? out of 202 examined corneae

The phenomenon was never seen in normals but only in relation to pathological conditions of the cornea, such as keratitis (herpetic cases of pronounced marginal keratitis) foreign bodies erosion vesicles central to pterygium and after 10 % cocaine

The permanent holes are of diagnostic value in practice The same is true of *Fischer-Schweitzer's* polygonal pattern and vital staining with fluorescein and rose bengal

These methods for studying the superficial corneal pathology *have been* briefly described

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CENTRAL SEROUS RETINITIS

A Follow up Study

BY

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Introduction

Retinitis centralis serosa or central serous retinitis is the designation employed for the eye disease which has been known by many names since v Graefe in 1866 described his central recurrent retinitis – or rather there have been a large number of descriptions of a disease picture which now must be considered to have referred to the same disorder The various designations also reflect the different interpretations of its aetiology It has been called among other things retinitis centralis (*Asayama* 1892) central serous chorioretinitis (*Masuda* 1916) preretinal oedema (*Gust* 1925) chorioretinitis centralis serosa (*Kitahara* 1936) central angiospastic retinitis (*Horniker* 1929) idiopathic flat detachment of the macula (*Walsh* & *Sloan* 1936) juvenile disciform degeneration (*Verhoeff* & *Grossman* 1937) retinal capillaritis (*Baillart* 1938) central angiospastic retinopathy (*Gifford* & *Marquardt* 1939) choriodosis centralis serosa (*Duggan* 1942) foveomacular retinitis (*Cordes* 1944) and serous disciform detachment of the macula (*Maumenee* 1959)

Central serous retinitis is taken to mean a disease – or perhaps rather a group of related diseases – characterized by fairly sudden onset of impaired central vision localized accumulation of serous fluid in the macular region and a tendency to complete cure as well as to recurrence

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The great majority of cases were originally reported from Japan but gradually it has been realized that the disease is not at all uncommon in Europe and America

Nearly all authors have reported that the disease shows a predilection for males in whom it is twice as common as in women As a rule the disease affects youngish adults who are on the whole in good general as well as ophthalmological health *Bennett* (1955) and *Straatsma* (1966) emphasized that the disease occurred especially in active energetic individuals in responsible jobs requiring good vision

The symptoms consist in an extremely varied degree of visual impairment positive or negative scotoma metamorphopsia micropsia and disturbances of colour perception The symptoms have been described in great detail by *Bruckner & Field* (1945) and *Amsler* (1953)

The objective signs are oedema in the central region with a surrounding annular reflex The macula is of varying colour usually a darker red than normal and often has small yellowish white spots at times there may be minute punctate haemorrhages Frequently the patients have transient hypermetropia which has been explained as a consequence of the forward bulging of the macula The metamorphopsia and demonstration of the scotoma may be utilized for diagnostic purposes *(Bruckner & Field* 1945 *Amsler* 1953) *Forsius et al* *Chilaris* (1962) *Magder* (1960) and *Paul & Batra* (1966) have described a dazzling or glare test measuring the time of restoration of vision after the eye has been dazzled by the light from the ophthalmoscope This period is prolonged in central serous retinitis

The duration of the disease is weeks or months sometimes longer and there is a marked tendency to recurrence As a rule the disease is unilateral but it may also be bilateral *Straatsma* (1966) stressed that all his bilateral cases developed recurrences in one or both eyes

Detailed clinical descriptions accompanying materials of varying size have been published by *Oguchi* (1922) *Harrington* (1944) *Cordes* (1944) *Duggan* (1942) *Gifford & Marquard* (1939) *Bennett* (1955) *Mitsui & Sakanasi* (1956) and many others From the point of view of definition and differential diagnosis the problem is mainly the relation to disciform macular degeneration *Klien* (1951 1956 1965) divided serous central retinitis into 3 types – retinal (central retinopathy) chorioretinal (central chorioretinopathy) and a deeper choroidal type (central choriopathy) *Duke Elder* (1966) feels that the third type should possibly not be included since it differs clinically from the others and has a poorer prognosis In his opinion it is identical with the disciform macular degeneration According to *Duggan* (1942) there is only a difference in degree between disciform degeneration and the milder lesions seen in central serous choriodosis which is his term for serous central retinitis *Maumenee* (1965) makes a distinction between a serous and a haemorrhagic type stating

also that an originally serous condition may develop into a haemorrhagic on with a poorer prognosis

The aetiology is as yet entirely unelucidated Macular oedema may complicate a number of eye diseases and has in particular been reported following cataract extraction (*Irvine* 1953 and others) Several hypotheses on toxic allergic metabolic infectious and vasomotor factors have been suggested *Hornaker* (1937) and *Gifford & Marquardt* (1939) emphasized vasomotor instability in the patients *Harrington* (1946) interpreted central serous retinitis as a psychosomatic disease

As far as the mechanism is concerned recent investigations using fluorescein angiography (*Norton et al* 1965 *Wessing* 1967) have claimed finding a defect in Bruch s membrane In obstinate cases *Wessing* has successfully used photocoagulation around this defect

Kranenburg (1960) emphasized a rare congenital malformation the papillary pit accompanied by scotomas and in about 30 % of the cases by central serous retinitis owing to vulnerability of the macula to various noxae

Numerous therapeutic measures have been employed without ever havin any definite effect This applies also to steroids

The prognosis is stated by most authors to be good but many recurrences may leave permanent visual impairment Here again it is a matter of definition *Wessing* (1966) states that the prognosis is favourable in the great majority of cases but that 5 % develop a condition which is indistinguishable from disciform degeneration *Bennett* (1955) makes a distinction between two groups – one large group exhibiting the picture of classical central serous retinitis and a smaller group in which the course shows that there has been question of macular degeneration All patients of the latter group were over 50 years of age *Duggan* (1942) too found the serious sequelae in persons over 50

Searching the literature the present author could find but one follow up study *Sverak Wassermannova & Peregrin (1960)* who reported a *follow up* on 36 out of a material of 50 patients with central serous retinitis at the end of 6 months to 10 years *They found normal ophthalmoscopic* appearances in 8 4 % delicate pigmentations and at times absence of normal foveal reflex in 22 2 % *and larger map like mainly superficial* foci with pigmentary disturbances in the macula of the originally affected eye in 69 4 % They supplemented their examination by Magder s glare test which revealed in the affected eyes a recovery period which was almost twice that in normal control eyes indicating that function in the affected eyes was still disturbed although all symptoms had disappeared Standard ERG showed significantly lower values of the scotopic b wave in both eyes

The ERG glare test showed also bilaterally that the period before the b wave returned to the initial value after dazzling was longer in the affected persons than in normal control subjects This sign of persistent *disturbance* of

scotopic as well as photopic retinal function is interpreted as a sign that in central serous retinitis there has been primary functional inferiority of the retina However these electroretinographic findings have not been confirmed by others (*Elenius* 1968)

Present Investigations

During the period 1958 1962 a total of 20 patients with central serous retinitis were seen in the Eye Department (including the Out patient Department) of the Copenhagen City Hospital This diagnosis had not been recorded previously in the diagnostic files The follow up period thus is a minimum of 5 years Out of the 20 patients 1 had died 1 is a sailor overseas but has sent a reply to a follow up letter All the others have been after examined

The diagnosis was based upon symptoms visual impairment positive scotoma and/or metamorphopsia as well as a typical ophthalmoscopic appearance All the patients but 1 who had fairly marked hypertension were in good general health and laboratory as well as X ray studies showed no abnormalities All the patients stated that previously their vision had been good apart from mild refraction anomalies However two reported that previously they had had similar attacks which had subsided

One of the patients exhibited a typical pit in the disc of the affected eye The others had no previously recognized eye diseases apart from mild refraction anomalies

Out of the 19 patients 13 were males and 6 females

Age distribution 3 patients were 20 29 years of age 7 were 30 39 6 were 40 49 and 3 were over 50

Only a few of the patients had attended the Out patient Department until all symptoms and signs had disappeared After the diagnosis had been made the *majority* were referred back to their own ophthalmologists Most of the patients received no treatment a few steroids for a short time

In accordance with precious publications we found the disease to occur mainly in youngish people in good general as well as ophthalmological health and th e was a male preponderance Another finding in accordance with previous authors was that the patients did not make up a representative section of the population but belonged predominantly to the *upper middle class* with a pronounced over representation of intellectuals (2 physicians 2 engineers 1 M A and 1 teacher)

Most of the patients did not remember much about their eye disease They merely had the impression that it had lasted some months and then gradually subsided

At follow up 13 stated that they had had no recurrence Two – Cases 8 and

15 – had experienced mild symptoms in the same eye as originally affected but none during recent years Two – Cases 10 and 18 – had had numerous recurrences of exactly the same nature as originally However in both cases the symptoms occurred now on one side and now on the other, and in neither case did the attacks grow less common or less severe Especially Case 18 felt greatly hampered by the incessant recurrences

Two patients – Cases 1 and 2 – differ somewhat from the others Their original attacks had subsided in a few months leaving good vision in the affected eye with slight metamorphopsia as the only symptom At the end of 9 and 7 years respectively they developed a new process in the originally affected eye but of a far more severe nature

Case 1 *developed in the macula a yellowish lesion almost as large as the* disc At the end of one year it is slightly pigmented marginally but otherwise appears to be *stationary There is a central scotoma and the* visual acuity is 6/18

Case 2 developed sensations of scotoma and marked deterioration of vision There were cicatricial changes in the macula and above the disc a persisting roundish prominent retinal detachment without tears The condition was interpreted as exudative retinitis possibly starting from the corner of a central serous retinitis

Present Complaints

8 patients reported having no visual complaints at all 7 had mild complaints mainly metamorphopsia noticed only when the patient was using the affected eye alone A few had a persisting scotoma which also did not annoy them in binocular vision and a few had subjectively slightly impaired vision

Only 4 had serious complaints This applies to the above mentioned Cases 1 and 2 as well as Cases 4 and 19 The latter two – the oldest patients of the *series – are the only ones in whom the attack* which led them to the Eye Department had never subsided but vision had gradually deteriorated as the years went by

Moreover Cases 10 and 18 – in spite of a good visual function in between *the attacks – are troubled by their numerous recurrences*

Objective Findings

The follow up examination of the 18 patients included *determination* of visual acuity slit lamp study measurement of ocular tension determination of the visual field and *ophthalmoscopy*

Visual acuity is good in most cases being in 12 patients 6/9 or better in several *6/4 5* Two have 6/12 and 6/18 respectively without major subjective

Table I

The patients

patient no	age	sex	side	year		recurrences
1 E L	40	F	right	1958		after 9 years
2 H A O	3[illegible]	M	right	–		serous detachment after 7 years
3 A R J	46	M	left	–	moderate hypertension	none
4 M T	54	M	right	–	similar attacks before never recovered after last attack	none
5 R M.	26	F	right	1959	similar attacks before	none
6 K L.	47	M	left	–		none
7 J H L	31	M	right	–		none
8 A B	38	M	left	1960	information by mail	3 mild recurrences
9 H M	40	F	left	–		none
10 N B	2[illegible]	F	left	–		several bilateral
11 H O J	3[illegible]	M	right	–		none
12 H M	29	F	left	–		none
13 S D	37	M	left	–		none
14 H O H	39	M	left	–		none
15 H M L	40	M	right	–		3 4 mild recurrences
16 C J J	57	M	right	1961		none
17 H M	37	M	left	–		none
18 F B	4	M	left	1962		several bilateral
19 M J C.	6[illegible]	F	left	–	never recovered	none

Table II
Follow up findings

present complaints	visual acuity	visual field	ophthalmoscopy
impaired vision	6/18	scotoma	yellow macular scar with pigmentations
impaired vision	hand movements	scotoma	macular scar flat detachment above the optic disc
impaired vision	6/18	scotoma	macular degenerations mainly in the left eye colloid bodies
impaired vision	6/60	scotoma	disciform degenerations in the right eye less pronounced degenerations in the left macula
scotoma	6/12	scotoma	slight pigmentation
none	6 6	normal	slight pigmentation
metamorphopsia	6/6	normal	yellow degenerative scar above and temporally to the macula
metamorphopsia			
none	6 6	normal	normal
none	6/6 right eye 6/4 5 left eye	normal	slight degenerations in both maculae small pigmentation in the left
none	6/6	normal	slight degeneration
scotoma	6/6	scotoma	pit in the left optic disc, colloid bodies in the macula
none	6/9	normal	normal
black spots	6 6	normal	slight degenerations in both maculae mainly the left
none	6/4 5	normal	slight pigmentations in the left macula
none	6 6	normal	slight pigmentations in both maculae
none	6 6	normal	colloid bodies
scotoma left eye	6 6 both eyes	scotoma	slight pigmentation slight oedema in the left macula
impaired vision	1/60	scotoma	huge degenerative senile changes mainly in the left eye

complaints in other respects Lastly there are the 4 above mentioned poor results with visual acuity of from 6/18 to hand movements

Visual field determination showed central scotomas in the 4 patients with poor function In addition there was a relative scotoma in 4 including the only patient of the material having a Kranenburg papillary pit

Ophthalmoscopy showed normal appearances in only 2 cases All the others had more or less marked central changes without any characteristic common features The findings varied from a slightly mottled pattern and small colloid bodies to more marked pigmentations and degenerations which could not be distinguished from incipient senile degeneration Case 4 had a pronounced punched out degenerative area in the centre as if left by a disciform degeneration Case 19 had enormous degenerations – mainly in the affected eye but also marked in the other eye where vision was well preserved Case 2 had pigmentations in the macula and a flat detachment above the disc

Tension proved normal and there was nothing remarkable in the anterior segment

Discussion

This follow up examination confirmed the previous impression that central serous retinitis is on the whole a benign disease However less than half the patients reported to have no manner of visual complaint after a follow up period of 5 10 years Several have fairly insignificant subjective complaints in th form of persistence of some of the original symptoms and follow up examination showed that the ophthalmoscopic appearances were not normal except in a very few

An entirely unsatisfactory visual function was present in two of the oldest patients who should no doubt be distinguished from the others in a separate group as done e g by *Bennett* Although they were originally interpreted as cases of central serous retinitis the course has revealed that more profound changes have been operative On the whole the relationship between central serous retinitis and disciform degeneration still remains unelucidated If there is a question of two entirely different affections it is at least difficult in a number of cases to draw a sharp clinical limit except by the course at long sight Presumably it is well to be wary of diagnosing central serous retinitis and thereby predicting a good prognosis in patients over 50 years of age

On the whole it seems reasonable to separate as does *Straatsma* all patients with systemic diseases as well as all patients who show in the course of the disease haemorrhagic elements in the retinal process in order to arrive at the pure cases of central serous retinitis – whether it is a disease *sui generis* or the

Table II
Follow up findings

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impaired vision	hand movements	scotoma	macular scar flat detachment above the optic disc
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scotoma left eye	6/6 both eyes	scotoma	slight pigmentation slight oedema in the left macula
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reaction of an already inferior retina to some irritant or other – as Kranenburg interprets the condition in patients with a congenital papillary pit

It is worth drawing attention to the two patients who ran the following course After their central serous retinitis of a typical course had subsided they kept well without any ocular symptoms apart from very mild metamorphopsia In this respect they are exactly like so many others of the same diagnosis However after an interval of 7 and 9 years respectively they developed macular affection in the same eye but of considerably more serious nature and with a more serious end result than the former This might indicate that even after an apparent cure the retina is left in a somewhat more vulnerable state than before It is going to be of interest to see how the others fare when they reach the age at which retinal changes of ageing become more common

The great majority of cases were unilateral but the two patients with bilateral involvement are the very patients who had the largest number of recurrences Possibly cases with many bilateral recurrences make up a group which differs fundamentally from that of the unilateral cases with no or few recurrences

Summary

19 patients with central serous retinitis were after examined after a follow up period of 5 10 years In two patients – both over 50 years of age – the course showed that there had been a question of disciform degeneration Two patients after enjoying a long period practically devoid of symptoms developed recurrences of a somewhat different nature and severity Lastly two patients have frequent bilateral but not violent recurrences and good function during the intervals The remaining patients have no or only mild complaints Nearly all have uncharacteristic ophthalmoscopic changes

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INTRAORBITAL MENINGIOMAS ENCASING THE OPTIC NERVE

A report of two cases

BY

EMIL ALS

According to *Reese* (1963) meningiomas constitute 17 % of all tumours of the central nervous system They are most often found parasagittally and in the cribriform tubercular and sphenoidal regions *(Bailey* 1948) but may originate anywhere from the dura on the inside of the cranium or from the falx and the tentorium Of special interest to the ophthalmologist are suprasellar presellar sphenoid ridge and orbital meningiomas

In a series of 230 consecutive cases of unilateral expanding lesions of the orbit *Reese* (1963) found meningiomas in 11 (5 %) In a series of 31 cases of orbital tumours *Dandy* (1941) found one with dural tumours of the orbit without positive roentgenograms of the skull This case was bilateral which is exceedingly rare In the majority of cases orbital meningiomas originate intracranially primary meningiomas of the orbit being comparatively rare

Craig & Gogela (1949) included as orbital meningiomas even those that arose within the confines of the optic canal and subsequently extended both intraorbitally and intracranially

The purpose of this paper is to report two cases of meningioma originating from the orbital portion of the optic nerve and surrounding it like a cuff

Case 1

A four year old boy was admitted to the Department of Neurosurgery in Lund late in

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1951 For over a month his parents had noted a progressive protusion of the right eye

Ophthalmological examination There was unilateral exophthalmos with the right eye protuding 4 5 mm compared to the left one The proptosis was non pulsating and irreducible but no tumour could be palpated in the orbit The pupil reacted normally

The nerve head was seen to be elevated approximately 4 dptr No hemorrhages were observed and no striae to imply pressure from behind The left eye was normal in every respect Visual acuity was RE 5/5 LE 5/4 (Sjogren s hand)

General examination and the otologist s inspection revealed nothing abnormal No signs of endocrine disorder were found

X rays of the skull and orbit gave no clue as to the nature of the process

Operation The orbit was explored by means of a transfrontal extradural approach The orbital portion of the optic nerve was entirely encased in a tube of tumour tissue that together with the nerve formed an approximately 7 mm thick string The tumour was radically removed together with the intraorbital part of the nerve It was deemed impossible to dissect the tumour free from the nerve As the tumour showed a tendency to invade the sclera great care was taken to divide the nerve as far anteriorly as possible which resulted in a piece of the sclera being removed A month later the optic canal was opened intradurally and the remaining part of the nerve was removed This part of the nerve showed tumour infiltration only in its most anterior portion the intracranial part of the nerve seemingly unaffected

Biopsy The optic nerve was almost completely enveloped by a meningioma of the fibroblastic type It showed a tendency to infiltrate the superficial fasciculi No signs of malignancy were found

For ten years following the operation the patient was regularly seen at the ophthalmological and neurosurgical departments At no time was there any sign of a recurrence of the tumour in the orbit or in the eye

In 1961 ten years after the orbital operation the patient was operated for a plexiform neurinoma of the spinal cord

Case 2

A 4 year old man was admitted early in 1968 to the neurological department in Lund He had complained of slight pain above his right eye for some time and attacks of blurred vision

Ophthalmological examination A right sided exophthalmos of 3 mm was found (in spite of the left eye being myopic and the larger one) The proptosis was non pulsating and irreducible Motility was normal The pupils were of normal size but the right one reacted somewhat sluggishly The nerve head was elevated 4 5 dptr There were small retinal hemorrhages and distended retinal veins The left disc was slightly myopically changed

Visual acuity was RE 6 6 LE 6 6 (−3 5 sph) The fields were normal except for an enlarged blind spot in the affected eye General examination and laboratory findings were normal

X rays of the skull were normal A right carotid angiography was also normal Jugular phlebography showed no filling of the right ophthalmic vein

Encephalography revealed a hardly descernible tumour in the region of the right anterior clinoid processus

Operation A tumour the size of a small seed was found intracranially representing an outgrowth through the optic canal of a large tumour surrounding the entire orbital

portion of the optic nerve The tumour was freed from the sclera by sharp dissection and radically removed together with the intraorbital part of the optic nerve Postoperative examination of the specimen showed that there was a distinct demarcation between the tumour and the optic nerve the latter being easily removable from the tube of tumour tissue when it was opened by a longitudinal incision

Biopsy The sheaths of the optic nerve were partially infiltrated by a meningioma of the psammomatous type The nerve proper was not infiltrated but showed signs of gliosis No malignancy was found

Comments

In these two cases the meningioma obviously originated in the orbit Both patients were young This agrees with the findings of *Hudson* (1940) that a meningioma from the orbital portion of the optic nerve is to a great extent a disease of young persons In his material 50% of these tumours occurred during the first two decades of life Thus this tumour seems to form an exception to the rule that the meningioma is in general a disease of middle age

In spite of considerable exophthalmos and heavy papilloedema the vision was only slightly affected if at all

Craig & Gogela (1949) did not find vision to be of aid in distinguishing meningiomas from other orbital lesions This is probably true as far as meningiomas with intracranial origin are concerned *Birge* (1955) and others have emphasized that unilateral loss of vision may be the first sign of meningiomas in the sellar region But as to tumours from the optic nerve sheaths within the orbit it is understandable that they may grow large and produce considerable exophthalmos without disturbing vision On the contrary if the tumour arises from the nerve proper as gliomas do vision is early and severely damaged

None of the present cases showed roentgenological changes of the skull According to *Rucker & Kearns* (1961) meningiomas in the region of the optic nerve and chiasm produce changes that are visible in skull roentgenograms in 85% of the cases This must apply to tumours with intracranial involvement rather than those confined to the orbits *Reese* (1963) presented a table of 21 meningiomas with exophthalmos Nine of them were located in the orbit and none of these had positive roentgenograms Furthermore they all had normal visual fields This is also in full agreement with the present findings

In case 2 it was found that the optic nerve was intact and could easily be removed from inside the tube of tumour tissue This rises the question if it would be possible to remove the tumour radically and spare the optic nerve Dandy attempted this in the case of bilateral tumours mentioned above but without success the growth being "so tenaciously bound and so deeply constricting the nerve that its removal was impossible In the present case 2 how

ever it seemed that radical removal with sparing of the optic nerve would probably have been technically feasible if attempted

Summary

Two young patients with cufflike meningiomas arising from the orbital portion of the optic nerve sheaths were reported In spite of considerable exophthalmos they lacked any definite impairment of vision Furthermore roentgenograms of the skull were normal These findings seem to be consistent with those of previous authors

In both cases the tumour was radically removed by the transfrontal approach together with the optic nerve The possibility to remove such tumours radically with sparing of the optic nerve is discussed

References

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DIE PROBLEMATIK DER ERWORBENEN MACULATRAKTION

VON

JOZSEF und ELISABETH BACSKULIN
(Mainz)

Obwohl die Problematik der Maculaverlagerungen ein so enormes praktisches *und theoretisches Problem darstellt* ist dieses Gebiet bisjetzt in der Ophthalmologie sehr mangelhaft bearbeitet Stanković ein hervorragender Kenner dieses Gebietes betont mit Recht dass noch viele Unklarheiten uber dieses sehr wichtige Problem herrschen

Dieses wird deutlich wenn wir einen kurzen Blick auf die bisherige spärliche Literatur werfen Vor kaum 12 Jahren fassten Horwich und Linfesty die samtlichen angeborenen und erworbenen Fälle auf 12 zusammen In den nachfolgenden Jahren haben vorwiegend Payne und Crick *Nauheim und Merrick* Rados und Scholz und besonders Stanković Bacskulin und Gibis sich mit diesem Problem eingehend beschäftigt und vor allem auf die Wichtigkeit der erworbenen Maculaverlagerungen hingewiesen

Während der Tagung der Rhein Mainischen Augenarzte in Frankfurt 1962 haben wir uber 23 Fälle von angeborenen und erworbenen Maculaverlagerungen berichtet (Unsere spateren Beobachtungen über insgesamt 36 Fälle – die im II Teil unserer *Arbeit uber Maculatraktion nach Lichtkoagulation* bearbeitet werden – haben unsere Ansichten nur bekraftigt)

Aufgrund unseres bisjetzt grossten Beobachtungsgutes und eingehenden Literaturstudiums haben wir die Maculaverlagerungen in 4 Gruppen eingesteilt

I Kongenitale Ektopien der Macula
II Heterotopien der Macula
III Perinatale (primare) Maculatraktion

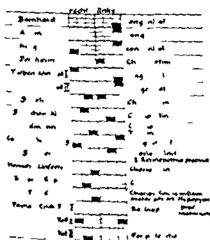
* Auszugsweise vorgetragen auf dem Kongress der Rhein Mainischen Augenarzte 1962 in Frankfurt und vor der Association for *Eye Research 1967 in London*

Eingegangen am 4 December 1968

IV Erworbene (sekundare) Maculatraktion (s Acta opth 1967)

Im Gegensatz zu den vorherigen Behauptungen haben wir schon 1962 aus drucklich darauf hingewiesen dass die Maculalage besonders zur Klassifizie rung von angeborenen und erworbenen Fallen eine ausserordentlich grosse Rolle spielt Bei Horwich und Linfesty konnte man wegen der sehr sparlichen Falle tatsachlich kein System aufbauen (s Abb 1 und Abb 2) Dagegen gelang es uns eindeutig zu beweisen dass bei der 1 und 2 Gruppe (kongenitale Ekto pien und Heterotopien) fast immer eine temporale Verlagerung der Macula bestand und bei der 3 und 4 Gruppe (primare und sekundare Maculatraktion) fast ausschliesslich eine nasale – meistens nasal untere – Maculatraktion ent stand Besonders grosse Bedeutung zeigte die Lage der Maculatraktion in pro phylaktischer und therapeutischer Hinsicht bei der Lichtkoagulation

Wegen des besseren Überblickes mochten wir zuerst die wichtigsten Eigen schaften der Maculaverlagerungen zusammenfassen



IV Maculatraction

			R	L	Anamnese und Bemerkungen
1	[illegible] 19..				[illegible] Operation
2	Friedmann 1958				T...
3	[illegible] Rope 1958				Co
4	Fould 19.6				Inflammat... [illegible]
5	Payne, Crick	... II			Periphlebitis (Diathermie ... [illegible])
6	Horwich Linfesty				Chorioretinit
7	Mauthner 1960	Fall II			Inflammatorisch
8		Fall V			[illegible] (... Lindau)
9	Bernhard	Fall I			Perip... [illegible]
10		Fall II			T... (Hämophthalmus ...)
11	E[illegible]	F. I I			[illegible]
12		Fall I			[illegible]
3		Fall II			Periphlebitis (L)
4		Fall III			[illegible]
15		Fall V			Periphlebitis (LK)
16		Fall VI			Periphlebitis ([illegible])
17		Fall VII			Periphlebitis ([illegible])
18		Fall VIII			[illegible] (T...)
9		Fall IX			T... (perf Verletzung LK)
20		Fall X			Hippel-Lindau (LK) [illegible]
21		Fall XI			Inflamm. toxisch (Pseudotumor
22		Fall ...			Macula foramen ([illegible])
23		Fall ...			Periphlebitis ([illegible])
24		Fall ...			[illegible]

Abb 1

Die Macula ist in alle Himmelsrichtungen verstreut und lasst bei den sparlichen Fallen ke n System e kennen (Der mittlere Quarant enspricht der nomalen Maculalage)

Abb 2

Be erworbenen Maculatraktionen ist die Macula immer nach nasal und meistens nach unten erlagert (Stelle der ursprunglichen Augenbeckerspalte)

1 Die Maculalage und die sorgfältige Anamnese erleichtern die Unterscheidung zwischen angeborenen und erworbenen Formen und deren Klassifizierung

2 Bei kongenitalen Maculaektopien sind öfters mehrere andere Missbildungen vorhanden

3 a Häufig Frühgeburten mit Sauerstoff behandelt (s Heterotopien bei Retinopathia praematurum)

b Meistens liegt ein Gefässprozess vor bei dem die gemeinsame pathogenetische Verwandtschaft in Hypoxydose liegt (DODEN)

4 a Bei erworbenen Maculatraktionen kann eine temporale Verlagerung nicht vorkommen S Abb 10

b Meistens ist die Macula gleichzeitig auch nach nasal und unten traktioniert (*Lage der ursprünglichen Augenbecherspalte Bacskulin*)

c Deshalb sind in prophylaktischer Hinsicht jegliche unnötige Manipulationen in Macula und Papillennahe – vor allem aber im temporal unteren Quadranten – zu vermeiden

c Durch das Zug Kontrazug Prinzip (s später) kann man einer starkeren Verziehung der Macula vorbeugen (Bacskulin)

5 Die Amotionen sind meistens flach und ohne Foramen Sie zeigen dreierlei Verziehungsmoglichkeiten der Netzhaut

a Netzhautfaltelung

b Netzhautrotation

c Netzhaut dehnung

6 Oft besteht ein erheblicher Netzhautastigmatismus (Bacskulin)

7 Trotz erheblicher Maculatraktion bleibt die Netzhaut im Maculabereich meistens anliegend

8 Nicht selten cystoide Maculadegenerationen

9 Der Visus ist nicht vom Grad der Maculaverlagerung abhangig (Bacskulin)

10 a Scheinbare excentrische Fixation trotz nachweisbarer (Durch Euthyskop) zentraler Fixation

b In manchen Fällen echten excentrische Fixation

11 Vorhandensein eines Pseudostrabismus meistens mit Hohendisparation

12 Oft wesentlich besseres Sehvermogen als der scheinbaren excentrischen Fixation entspricht

13 a Allgemeine abnormale Verziehung der Retinogefasse

b Indirekte Maculavascularisation

14 Auffallig abnormaler Winkel Gamma

15 Ungleichheit der Schielwinkel zwischen dem Abdeck Test und der Perimetermessung

16 Abnormal verlagerter blinder Fleck

17 Haufig Differenz des Hornhautscheitelwertes von 2 bis 5 mm

18 Die subjektiven Beschwerden sind charakteristisch *Sehstorungen* unge

wöhnliche Schielstellungen Diplopien Verlust des Binocularsehens Verzerrt sehen unphysiologische Aniseikonien manchmal sogar schiefe Kopfhaltung u a

Wegen der Überlange des Materiales möchten wir auf eine ausführliche Besprechung der samtlichen Falle verzichten und verweisen auf unsere Thesis von 1963 An Hand eines typischen Falles möchten wir in der Besprechung folgen de Problematik verstandlicher machen

Sch Wilhelm 25 jahriger Schmied Fruher mit beiden Augen gut gesehen und fruher keine Schielstellung gehabt (s Abb 3 a und 3 b) 1953 und 1954 langere stationare Aufenthalte in der Univ Augenklinik Marburg wegen Periphlebitis links Damals bestand links im Maculabereich eine recidivierende Korpusblutung Zuletzt fanden sich z T prominente Narbenbezirke mit bindegewebigen Verschwartungen Damals wurde erwahnt Es besteht die Moglichkeit einer beginnenden Traktions Amotio Visus rechts 5/4 und links cyl -1 0 Achse 0 = 5/20

Am 26 2 1962 Contusio bulbi links (Draht ins Auge geschnellt) mit Glaskorperblutung und Sehherabsetzung links auf Handbewegungen Bei der stationaren Behandlung konnte der Blutungsherd nicht festgestellt werden Am 12 6 1962 Wiederaufnahme wegen Sehverschlechterung Gleichzeitig Maculatraktion links *festgestellt Neben alten* periphlebitischen Veranderungen mit Einscheidungen und Traktion sowie peripheren Degenerationsstellen fanden wir bei 10 Uhr ein anliegendes Netzhautforamen Die linke Macula war etwa 2 Papillendurchmesser (PD) *nach nasal unten* hin verzogen mit abnormalem Gefassverlauf und rechtwinkeliger Abknickung der Vasa temporalis supe



Abb 3 a b

16 jahr Junge ohne Schielstellung

Der gleiche Mann 9 Jahre spater mit Pseudostrabismus nach Maculatraktion bei Periphlebitis

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b Netzhautrotation

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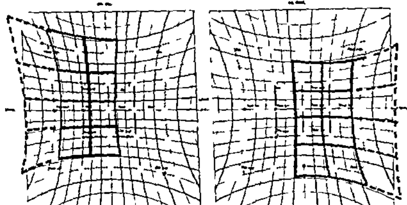


Abb 5
Hess Schema vom gleichen Fall

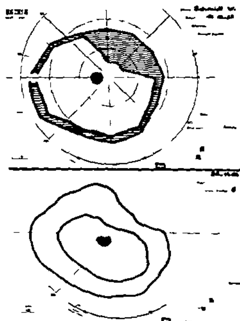


Abb 6 a b
Goldmann mit normalem blinden Fleck 1953 nach Untersuchung in der Univ Augenklin k Marburg
9 Jahre sp ter typ sche Verlagerung des blinden Fleckes nach Maculatraktion (Univ Augenklinik – Heidelberg)

rior (s Abb 4) sowie einer indirekten Maculavascularisation und deutlicher Pigmentverschiebung im Maculabereich ausserdem mit bogenformiger Netzhautfalte nach beginnender Retinitis proliferans Im unteren Bereich dichte Glaskorperdestruktion und trubungen Das rechte Auge war unauffallig Visus rechts 5/5 und links +1 0 cyl −2 5 Achse 0 = 5/10 p und Nieden II (Javal beiderseits o B)

Beim Blick geradeaus fiel eine ungewohnliche Schielstellung auf wobei das linke Auge neben Divergenzstellung deutlich nach unten deplaciert war (s Abb 3 b) Synoptophor Obj Winkel ≈ 20 Grad div und 5 Grad + VD Subj Winkel = 20 Grad div und 9 Grad + VD Keine Fusion Links Suppression Kleines Hemmungsskotom von wenigen Graden − Bei der Prufung mit dem Rotglas wurden gekreuzte und hohendifferente (im Sinne eine + VD) Doppelbilder angegeben deren Abstand in allen Blickrichtungen gleich blieb Dasselbe Ergebnis zeigte die Prufung am Hess Schema (s Abb 5) − Parallelstand nach Prismeausgleich wurde erreicht nach Vorsetzen von 8 P dptr Basis unten und 25 P dptr Basis innen vor das linke Auge (Ausserdem wurde subj Verzerrtsehen angegeben) − Hertel Werte bei Rechtsfixation rechts 17 und links 19 mm bei Linksfixation rechts 21 und links 18 mm bei Basis 102 Am Bjerrum Schirm war eine deutliche Verlagerung des blinden Fleckes nach unten und leicht nach nasal nachweisbar (s Abb 6 a) Dagegen war eine Verlagerung des blinden Fleckes seinerzeit in Marburg noch nicht vorhanden gewesen (s Abb 6 b) − Tension und Gonioskopie normal Die allgemeine Durchuntersuchung ergab Normale Sella Spezial und Rhese Aufnahme GT Test 1 10 000 pos Sabin Feldmann Test Komplementbindungsreaktion sowie Leptospirose Test neg TEG mit langer R Zeit Prothrombin Faktor VII o B und Prothrombinverbrauch gerade ausreichend Blutungszeit und Quick Wert normal Thrombocytenfunktion 3 (Grenzwert)

Bei diesem Fall standen wir vor einem grossen Problem bei der Begutachtung in Bezug auf den Unfallzusammenhang und Maculatraktion



Abb 4

Fundus von Abb 3 mit rechtswinkeliger Abknickung der Gefasse und erheblicher Maculatraktion nach nasal Unten Nach Korrektur eines hochgradigen Netzhautastigmatismus fast voller Visus

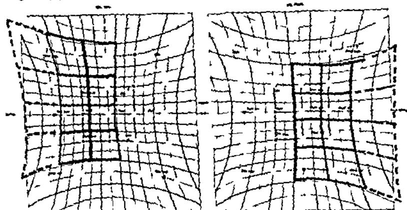


Abb 5
Hess Schema vom gleichen Fall

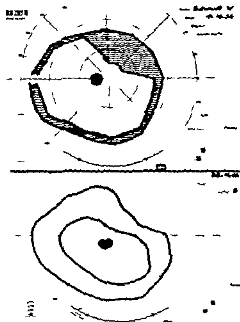


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9 Jahre spater typische Verlagerung des blinden Fleckes nach Maculatraktion (Univ Augenklinik – Heidelberg)

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Abb 4

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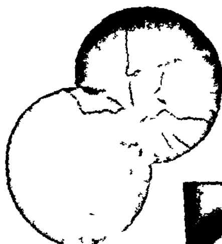




Abb 7 a b
Starke Deviation und Retraktion samtlicher Gefasse nach temporal unten mit nasal unterer Maculatraktion nach Korpusblutung
Gleicher fall mit entsprechendem Pseudostrabismus

immer nach nasal unten finden Deshalb sollte man in *temporal unteren Quadranten in Maculanahe moglichst jede Manipulation* – wenn nicht unbedingt notig – vermeiden oder gleichzeitig an kontralateraler Stelle durch Lichtkoagulation im Sinne der Zug Gegenzugwirkung einer Maculatraktion und deren schweren Komplikationen vorzubeugen (Bacskulin)

Auf das *Zug Kontra ugprin ip* kamen wir zufalligerweise nach unserem 11 Fall in Heidelberg Ein 23 jahriger Arbeiter erlitt eine perforierende Sklera verletzung am linken Auge im temporal unteren Quadranten unterhalb der Macula Nach der operativen Versorgung – wobei die Perforationsstelle durch ausgiebige Diathermiekoagulation abgeriegelt wurde – fanden wir am gleichen Auge an kontralateraler Stelle temporal oben von der Macula ein anliegendes Netzhautforamen Der Patient wurde dehalb zur Univ Augenklinik nach Bonn uberwiesen wo das Foramen durch Photokoagulation abgeriegelt wurde Es kam zu einer sehr geringfugigen Maculatraktion nach nasal unten Gleichzeitig konnte man aber deutliche radiare Netzhautfaltelungen zur kontralateralen

Bei der Suche nach kongenitalen Missbildungen – wobei wir uber 70 000 Patienten systematisch untersuchten – stiessen wir auf einige sehr interessante Fälle von erworbenen (sekundären) Maculatraktionen Wahren unserer Besuche an 54 europäischen und amerikanischen Univ Augenkliniken bekamen wir freundlicherweise mehrere schöne Fälle zur Verfügung womit unsere Anschauungen – insbesondere des *Zug Kontrazug Prizipes* – nur bestatigt wurden Bald *stellte sich heraus dass die erworbenen Maculatraktionen praktisch das gleiche* Symptomenbild zeigen wie die – angeblich – sehr seltenen Maculaektopien und Heterotopien Dauberhinaus wiesen sie auf eine wesentlich wichtigere praktische und theoretische Bedeutung hin Es stellte sich heraus dass sie wesentlich öfters vorkommen als man dies aus der bisher spärlichen Literatur annehmen konnte

Daran sind allerdings noch einige andere Faktoren beteiligt

Die wesentlich vollkommenere behandlung der Netzhautchirurgie wobei man auch *Partiell*-*Heilungen antrifft (Stein Stankovic Cibis Bacskulin)*

Die Einfuhrung der Lichtkoagulation als prophylaktische und therapeutische Methode die sorgfaltige Dokumenattion der Perphlebitiden das langere Überleben der Diabetiken und dadurch häufigeres Auftreten schwerer Fälle von Retinitis proliferans die zunehmenden Fälle von Verletzungen and anderes mehr

Es ist sehr auffallig dass bei allen Fällen von Gruppe IV (ausser Nr III) die Macula durch Traktion nach nasal[1] verlagert ist (s Abb 2) Bei diesen Fallen können wir meistens eine strangartige Traktionsfalte finden die mit den Maculaverziehungen in direkter Beziehung stehen (s Abb 4 und Abb 7a) Deshalb haben wir die Bezeichnung Maculatraktion vorgeschlagen Es ist sehr merkwurdig dass in den meisten Fällen die bandartigen Glaskorperstrange die durch Traktion zu sekundären *Maculaverziehungen fuhrten sich ungefahr* an der Stelle befinden die der ursprunglichen Augenbecherspalte entspricht *(s Abb 4 und Abb 7a) Das ergab einen sehr wichtigen prophylaktischen* und therapeutischen Wert In vielen Fallen konnten wir bei akuten Netz Aderhaut entzundungen beobachten dass sich eine Papillenunschärfe im temporal unteren Quadranten verbreitert Es ist nicht selten dass sich ein peripapillares Oedem restlos zuruckbildet jedoch bleibt noch immer ein passageres Oedem im beschriebenen Quadranten das stellenweise die Netzhautgefasse begleitet Es sind sicher nicht nur die statischen Komponenten dafur verantwortlich dass bei exsudativen Prozessen und auch bei Korpusblutungen gerade dieser temporal untere Quadrant standig am meisten betroffen ist Die vitrooretinalen bzw die *vitreovascularen Adharenzen spielen in* diesem Gebiet wahrscheinlich ebenfalls eine Rolle da sich die Entwichlung der temporalen unteren Gefasse an ihrer endgultigen Stelle am spatesten vollzicht (Badtke) Wenn man dass alles berucksichtigt ist es sicher *kein Zufall mehr dass die* Maculatraktionen sich fast

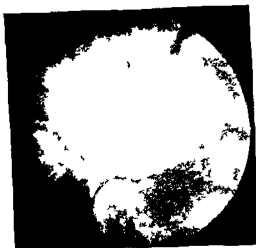


Abb 8
Fast totale Amotio Nur im verlagerten Maculabereich blieb die Netzhaut anliegend s Text)

(wie in unserem Fall II) oder ein postamotioneller Zustand und ahnliches mit vorubergehendem unbrauchbaren Visus

2 Ob es inzwischen schon zu einem Strab div ex anopsia gekommen ist

3 Wie weit sich der Visus spontan oder mit Korrektur bereits normalisiert

4 Wie waren die vorherigen allgemeinen optischen und orthoptischen Verhaltnisse – (Auch die evtl physiologischen und unphysiologischen Aniseikonien – (Sachsenweger Bacskulin)

5 Wie stark ist die entstandene Hohendisparation geworden usw – Die Hohendisparation ist nicht nur von dem Grad der Maculaverlagerung abhängig – (Stanković Bacskulin)

Durch die verlagerte Macula erhalten wir das Bild eines Pseudostrabismus Augenmuskelstorungen sind dabei meistens nicht vorhanden und zwar weicht das Auge jeweils nach der Richtung ab in der die Macula verlagert ist. Bei nach temporal verlagerter Macula resultiert ein Strabismus divergens Voraussetzung dafur ist jedoch das Vorhandensein des Binocularsehens Besteht eine Verlagerung nach oben oder unten so ergibt sich ein Hohenschielen. Nach Rados Nauheim u a ist der Grad der Verlagerung durch den Cover Test zu ermitteln und entspricht etwa (mit Berucksichtigung des Winkel Gamma) dem Schielwinkel der sich bei der Messung am Perimeter ergibt wenn zusatzlich kein Strabismus vorliegt Je nachdem kann der Schielwinkel ein gleiches oder ein entgegengesetztes Vorzeichen haben

Richtung zur Photokoagulationsstelle feststellen Trotz ausgiebiger Diathermie *koagulation im gefährlichen temporal unteren* Quadranten entstand keine nennenswerte Maculatraktion und kein Pseudostrabismus Auch bei späteren Kontrollen war die Maculalage praktisch unverändert Die Macula befand sich zwischen 2 Traktionsbändern die die Macula in einander entgegengesetzter Richtung zogen Damit war die Macula – *wie ein Kind im Kinderwagen* – in 2 entgegengesetzten Richtungen befestigt

In jedem Fall von Maculatraktion und auch bei Heterotopien finden wir einen sehr merkwürdigen Gefässverlauf (s *Stanković, Bacskulin Cibis* und Abb 4 und 7)

Wie wir schon darlegten konnten wir in mehreren Fällen (bei allen unseren Gruppen[1]) eindeutig beweisen dass die Sehverschlechterung nicht vom Grad der Maculaverlagerung abhängig ist Z B war die Macula in manchen Fällen *2 bis 3 PD nach unten und nasal traktioniert und wir konnten trotzdem nach* Korrektion eines früher nicht berücksichtigten Hochgradigen Netzhautastigmatismus fast volle Sehschärfe erreichen! Andererseits fanden wir aber bei leichten Verziehungen von ½ bis 1 PD eine Visusherabsetzung auf 1/50 (Gläser bessern nicht) Diese unsere Behauptung wurde von Badtke Doden Cibis François *Meyer Schweickerath Stanković u a ebenfalls bestätigt*

Dass ein Netzhautastigmatismus in diesem Fällen vorliegt beweist auch die Tatsache dass die Patienten die früher keine Brille trugen oder nur ein sphärisches Glas benötigten nach der Maculatraktion öfter nur mit *steigendem Cylinderglas* zu korrigieren waren – obwohl bei diesen Patienten sich sowohl *mit dem Javal als auch mit dem Refrakotmeter und der Skiaskopie* in Homatropin keine nennenswerten Astigmuswerte ergaben

Es ist sehr merkwürdig dass die Macula nicht selten mit grau gelblichem Granulationsgewebe bedeckt und der zentrale Visus unter 1/50 herabgesetzt ist Dabei geht manchmal trotzdem lange Zeit vorbei, bis der Patient anfangt *sich excentrisch zu orientieren Ebenfalls finden wir nicht selten* cystoide Maculadegenerationen Wenn die Netzhaut langere Zeit abgehoben war resultiert dies selbstverständlich im Visus Andererseits konnten wir gerade bemerken dass die Netzhaut im Maculabereich trotz der Maculatraktion – wahrscheinlich auch durch Begleitinflammation – ziemlich fest haften wie dies in unserem ersten *Fall mit fast totaler Amotio vorlag* Neben der Papille war die Netzhaut praktisch nur noch im Maculabereich *anliegend (s Abb 8)*

Die Entstehung des Pseudostrabismus bei Maculatraktion ist sehr kompliziert und on sehr vielen Faktoren abhängig Ausserdem bestehen nicht nur grosse Unterschiede in der Entstehungtart sondern auch in der ganzen Erscheinungsform kann bei Maculatraktionen gegenuber Maculaektopien und Heterotopien ein ganz verschiedenes Bild vorhanden sein Nur auf einige Möglichkeiten mochten wir hier hinweisen

1 Es ist viel davon abhangig wie lange eine dichte Korpusblutung besteht



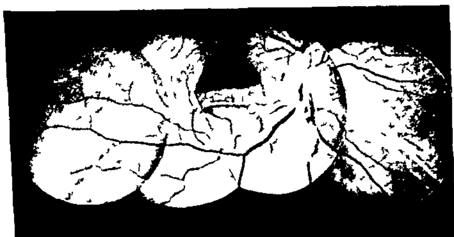


Abb 9 a b
Nasale Maculatraktion bei schwerer Retinitis proliferans bei Periphlebitis Breite und flache Traktionsamotio unten Nach langer 1 jähriger stationarer und hohenklimatischer Behandlung als aussichtslos nach Hause entlassen
Die gleiche Patientin 3 Jahre spater ohne jegliche Behandlung mit spontanlen Wieder anlegungsstreifen Nach Korrektur des hochgradigen Netzhautastigmatismus 5/10 bis 5 7 patiell Visus aber keine Rezidive mehr

gut und nicht im Schrifttum und noch weniger in fremden Kliniken Umso mehr mussen wir an dieser Stelle herzlich all denen danken die uns ohne Zogern ihr gesamten Krankengut zu dieser Problematik uberlassen haben

Daraus ergeben sich wesentliche Gesichtspunkte für die *Therapie* Nach Nauheim und Merrick muss jeder Fall individuell behandelt werden Wenn wir vom ätiologischen Standpunkt aus das Problem betrachten (s Abb 2) so begegnen wir verhältnismässig vielen Fällen von Maculatraktionen nach Photocoagulation sowie bei Chorioretinitis Toxoplasmose Hippel Lindau Coats und andere Retinopathien sowie *posttraumatische Prozesse.*

Es ist merkwürdig dass die Periphlebitis sowohl bei anderen Verfassern wie auch im ersten Teil unserer Arbeit (bis 1963) als häufigste Ursache der Maculatraktion angesehen wurde Das hängt teilweise damit zusammen dass wir bis zu dieser Zeit mehrere systematische Duchuntersuchungen in speziellen höhenklimatischen Augenheilanstalten vorgenommen hatten Andererseits scheint dass die Zahl der Periphlebitiden besonders mit diffusen Corpusblutungen in den letzten Jahren wesentlich seltener geworden ist Aber anscheinend hat sich die Periphlebitis nicht nur in ihrer Frequenz sondern auch in *ihrem Wesen viel geändert Deshalb* möchten wir die Therapieerfolge einiger Verfasser mit Vorbehalt betrachten

An dieser Stelle möchten wir einen besonders interessanten Fall kurz erwähnen

B G 23 jahr Frau wurde 1958 in der Univ Augenklinik Giessen wegen Periphlebitis am rechten Auge behandelt und anschliessend wegen Retinitis proliferans in das Augensanatorium Hochenschwand (Schwarzwald) uberwiesen

Am 26 11.59 wurde die Patientin trotz aller Bemuhungen nach Hause entlassen als aussichtslos (s Abb 9 a) mit einer deutlichen Maculatraktion nach nasal oben mit unbrauchbarem Visus und entsprechendem Pseudostrabismus Neben strangformigen Proliferationsschleiern am hinteren Pol fand sich eine breite und flache Traktionsamotio im unteren Bereich ohne Foramen die trotz Behandlung unverandert blieb Da die Patientin ihren Wohnsitz geandert hatte so gelang es uns nur mit Muhe sie 3 Jahre später in die Univ Augenklinik Heidelberg zur Kontrolle zu bestellen Zu unserer grossen Überraschung fand sich trotz jeglicher Behandlung ein praktisch abgeheilter Fall mit spontanen Wiederanlegungsstreifen und 5/10 bis 5/7 partiell Visus sowie ein erheblicher Netzhautastigmatismus (s Abb 9 b) Orthoptische Status Cover Test Latente Divergenz in der Nahe und keine Abweichung in der Ferne Prismen Cover Test In der Nahe 10 dptr Basis innen Motilitat regelrecht 11 bis 12 Grad Convergenz Am *Synoptophor sehr geringe Fusionsbreite* bei normaler Korrespondenz und vorhandener Stereopsis Kein Anhalt fur Diplopie Hertel Rechts 15 5 und links 17 0 mm bei Basis 96 mm Auch bei späteren Kontrollen ergab sich der gleiche praktisch beschwerdefreie Zustand mit kaum merkbarem Pseudostrabismus

Die zahlreichen Falle von Maculatraktionen nach Photocuagulationen die wir bisjetzt fanden zeigen deutlich dass sie wesentlich ofters vorkommen als man das aus dem bisher sparlichen Schrifttum annehmen konnte Den Grund hierfür hat uns *Paul Cibis* (1962) in einem Brief besonders deutlich ausgedruckt "Wenn Sie richtig suchen so finden Sie noch mehr Maculatraktionen nach Photokuagulation als Sie erwartet haben Aber suchen *Sie* im eigenen Kranken

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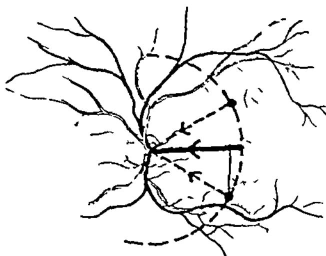


Abb 10
Bei Erwachsenen kann eine temporale Verziehung der Macula nicht vorkommen da die Netzhaut am Papillenrand stark fixiert ist

Besonders herzlichen Dank an Herrn Prof Cibis sowie die Herren Professoren Best Doden Meyer-Schwickerath François und Stanković sowie Herrn Adalbert Paulitschek SWF fur die Fotoabzüge

Zusammenfassung

Durch eingehendes Studium aller bisher uns erreichbaren Falle haben wir die Maculaverlagerungen in 4 Gruppen eingeteilt 1 kongenitale Ektopien 2 Heterotopien 3 Perinatale und 4 erworbene Maculatraktionen Die erworbenen Maculatraktionen stellen den Augenarzt vor ein sehr schweres ophthalmo chirugisches Problem wobei präventiv mit Zug Kontrazug Prinzip mehr zu erreichen ist als therapeutisch Die wichtigsten Eigenschaften der Maculaverlagerungen wurden in 18 Punkten zusammengefasst

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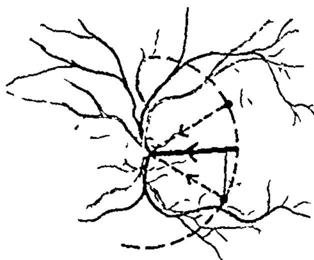


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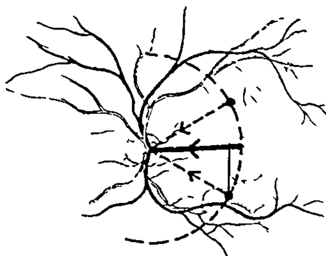


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facility of the second eye 0 030 c. mm/min/mmHg with a standard error of ± 0 01

In the case when the hydrodynamic equilibrium of the eye has been disturbed by any artefical intervention the intraocular tension endeavours to reach the original level the rate of equalisation is diminishing when the intraocular pressure value is approaching the original level The duration of equalisation varies between 10 to 30 minutes depending on the method applied (*Davanger & Holter* 1967) It might be 10 to 30 minutes (*Armaly & Halasa* 1963) 20 minutes (*Langham & Eisenlohr* 1963) 12 21 minutes on the average (*Chandler* 1964) more than 18 minutes (*Stepanik* 1962) and 25 to 30 minutes (*Tonjum* 1966) Thus it seems to be doubtful whether the 20 to 30 minutes rest between the tonographies of both eyes is enough especially when performing the tonographic test of Leydhecker This augments the duration of tonography in the case of an individual patient to at least one hour

To shorten the duration of tonography the method of bilateral tonography has been elaborated in the I Eye Clinic of Budapest

Methods and Clinical Material

With the synchronous bilateral application of tonometers the problem of fixation arises in an increased degree *Bedwell* (1966) has described an electronic indentation recording tonometer to which a transparent plunger has been constructed to aid fixation

For bilateral tonography 2 electronic indentation tonometers of Schwarzer have been used One of the plungers has been perforated in axial direction (hole diameter 0 8 mm) The construction of the Schwarzer electronic tonometer has made this perforation possible the loss in plunger weight has been compensated by adding weight to the plunger (the new plunger weight was 5 485 g) The tonometer head conforms to the requirements of the 5th Specification for Electronic Schioetz tonometers of the American Committee on Standardisation of Tonometers

According to the experiences with bilateral tonography so far the light beam piercing through the hole of the plunger coming from any light source might be sufficient for fixation

The 2 electronic tonometers used for bilateral tonography were not from the same series of production (type Z 10 /1 F No 0038 and 0104) their output levels in the identical scale reading range differed from each other to some extent To assure synchronism of the signals the output levels have been equalised by potentiometers

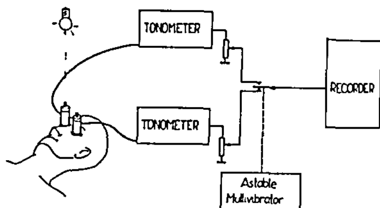


Figure 1
Block diagram of the measuring and recording arrangement of bilateral tonography

The block diagram in *Figure 1* represents the measuring and recording arrangement of bilateral tonography The tonographies of the two eyes have been recorded on the same channel in order to eliminate drift problems The equalised signals have been joined up with the DC channel of a recorder (Physioscript PST GS 312 of Schwarzer) through an electronic switch

This switches the signals coming from the 2 tonometers one after the other and links them with the input of the recorder One period is made approximately in 1 sec with an assymetric distribution of 1/3 to 2/3 within one period The assymetry was needed to be able to discriminate the tracings of the two eyes

The switching is made by an electromagnetic relay controlled by a transistorized astabile multivibrator As seen from the conditions of switching the duration of signal reversal is long enough that any direct recording stylus should conveniently follow the rate of switching In the mean time the sampling is fine enough compared with the changes during tonography thus the curves of both eyes are well valuable and are free of distortion

The cca 1 sec period roughly equals to the duration of one corneal pulse wave synchronous with the cardiac cycle This causes phase shift producing noisy appearance of the tonographic tracing When the pulse amplitude gets higher the noise also increases The noise caused by the 1 sec period of switching is needed for supervision of the appropriate position of the tonometers on the corneas *(Figure 2)*

The tonometers are held on the corneas by the aid of double stirrup frames fixed on the forehead The tonometers may freely move in the frames which causes them to travel together during fixation movements of the eyes The lids are separated by light plexigum straddles similar to that of the van Beuningen

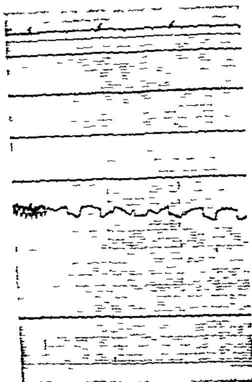


Figure 2

A portion of a bilateral tonogram showing the phase shift produced by the cca 1 sec period of the switching of the signals of the 2 tonometers

contact glass for gonioscopy The synchronous application of both tonometers on the eyes in the same instant does not mean difficulties after some practice

Figure 3 demonstrates the calibration curve of both tonometers done in the same time as the control of the coincidence of calibration levels of the instruments The performing of the tracing happens so that first the scale of the first instrument is made then the same scale is adjusted on the other instrument letting the curves run together for a while afterwards

With this method the bilateral tonographies of 20 young healthy volunteers have been carried out The age of the patients varied between 20 to 30 years The coefficient of scleral rigidity was around the normal value There was no refractive error exceeding ± 1 0 D the radius of corneal curvature was 7 8 ± 0 1 mm Topical anaesthesia was carried out by using 0 4 per cent Novesin solution The initial intraocular tension was equal in both eyes at the beginning of the tonographies

The tonography was uniformly carried out by using the 5.5 g plunger weight.

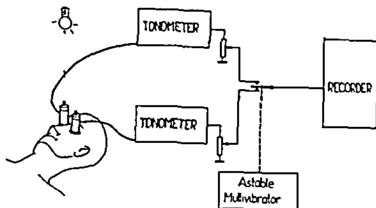


Figure 1
Block diagram of the measuring and recording arrangement of bilateral tonography

The block diagram in *Figure 1* represents the measuring and recording arrangement of bilateral tonography. The tonographies of the two eyes have been recorded on the same channel in order to eliminate drift problems. The equalised signals have been joined up with the DC channel of a recorder (Physioscript PST 6S 312 of Schwarzer) through an electronic switch.

This switches the signals coming from the 2 tonometers one after the other and links them with the input of the recorder. One period is made approximately in 1 sec with an assymetric distribution of 1/3 to 2/3 within one period. The assymetry was needed to be able to discriminate the tracings of the two eyes.

The switching is made by an electromagnetic relay controlled by a transistorized astabile multivibrator. As seen from the conditions of switching the duration of signal reversal is long enough that any direct recording stylus should conveniently follow the rate of switching. In the mean time the sampling is fine enough compared with the changes during tonography, thus the curves of both eyes are well valuable and are free of distortion.

The cca 1 sec period roughly equals to the duration of one corneal pulse wave synchronous with the cardiac cycle. This causes phase shift producing "noisy" appearance of the tonographic tracing. When the pulse amplitude gets higher the "noise" also increases. The "noise" caused by the 1 sec period of switching is needed for supervision of the appropriate position of the tonometers on the corneas *(Figure 2)*.

The tonometers are held on the corneas by the aid of double stirrup frames fixed on the forehead. The tonometers may freely move in the frames which causes them to travel together during fixation movements of the eyes. The lids are separated by light plexigum straddles similar to that of the van Beuningen

Table I

Mean values and standard deviations of the outflow coefficients and outflow numbers *of bilateral tonographies in 20 young healthy volunteers (11 females and 9 males)*

Number of tonographies	Tonography of Grant		Tonography test of Leydhecker	
	C_{0-4}	P_0/C_{0-4}	C_{L3-7}	P_0/C_{L3-7}
40	0 39 ± 0 06	49 ± 24	0 19 ± 0 03	62 ± 21

The same values for unilateral tonography in a normal population (Leydhecker 1957)

Number of tonographies	Tonography of Grant		Tonography test of Leydhecker	
	C_{0-4}	P_0/C_{0-4}	C_{L3-7}	P_0/C_{L3-7}
100	0 28 ± 0 07	54 ± 24	0 17 ± 0 04	56 ± 31

Conclusions

On the basis of experiences so far bilateral *tonography* seems to be a method recommendable for clinical practice

The *patients found the bilateral tonography to be better tolerable* than the classical onesided tonography The cause of this might be that both eyes were anaesthetised *at the same time the impulse for blinking* diminished and the irritable sensation of desiccation of the anterior surface of the globe present with the fixating eye during unilateral tonography was absent

The diminished standard deviations with bilateral tonographies compared with the standard *deviations in the literature population suggests the bilateral* tonography be more uniform

According to the views of *Boles Carenini Spurgen Buten & Ascher* (1955) the outflow resistance is somewhat higher at the left side with male patients With female patients such a side difference could not be found In our cases the male patients had more equivalent tonographic parameters at both sides than the female patients with normal *menstrual cycles* This phenomenon needs further investigations

Of course when the method gets accepted as a *routine* clinical examination investigations of the statistical normal values are required

The intraocular hydrodynamic and viscoelastic changes taking place during bilateral tonography cannot be evaluated yet therefore the increase of number of examinations would be desired too

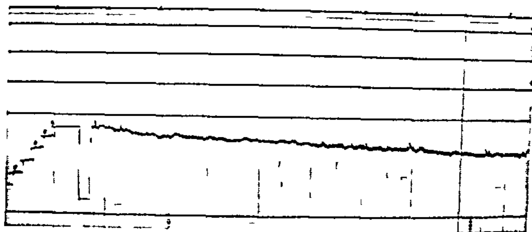


Figure 3
Calibration curve of the 2 tonometers and a sample of bilateral tonogram of a young male volunteer the recordings of both eyes seem to rival with each other

Results

Figure 3 shows a tracing of bilateral tonography In all cases the curve was more linear from a practical point of view than we are accustomed to in the case of the classical unilateral tonography Especially the exponential drop of the curve failed in the first minutes The intraocular pressure fluctuations in connection with respiration and the Traube Hering blood pressure waves are well pronounced

Table 1 shows the mean values and standard deviations of the outflow coefficients and outflow numbers calculated for the tonography of Grant (0 to 4 minutes portion of tonography) and for the tonography test of Leydhecker (3 to 7 minutes portion of the tonography) The calculations were made by using the calibration of *Friedenwald* 1955 The parameters of bilateral tonographies are compared to the parameters of unilateral tonographies of a normal population reported by *Leydhecker* The mean values of outflow coefficients of bilateral tonographies are somewhat higher than those of the literature population whereas the standard deviations are somewhat lower in spite of the fewer number of examinations In these cases the male patients had more equivalent tonographic parameters at both sides than the female patients

On the basis of examinations so far it could be shown that in female patients having normal menstrual cycles the curves of the two eyes had different gradients i e different outflow coefficients in spite of equal intraocular tension values at the beginning of tonography

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Authors address I Eye Clinic of the Med University VIII Illés u 15 Budapest, Hungary

Summary

Indentation tonographies have been simultaneously carried out on both sides by the aid of van Beuningen electronic tonometers The tonographies were recorded by means of the method of "electronic switch" after the equalisation of the output signs of the two electronic tonometers The results of bilateral tonographies of healthy volunteers are discussed

Acknowledgement

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mus spricht man dann wenn sich nur histologisch ein Bulbusrest nachweisen lässt

Differentialdiagnostisch können Ptosis Enophthalmus Mikrokornea und die entzündlich bedingte Verkleinerung des Auges – die Phthisis bulbi – zu Verwechslungen mit einem M führen Bei *M mit Spaltmissbildungen* sehen wir kolobomatöse Veränderungen der Iris Aderhaut Netzhaut der Makula und des Sehnerven Daneben sind alle weiteren Missbildungen des Auges möglich wie wir sie auch in der Gruppe 3 *M ohne Kolobombildung* finden Neben stark entwicklungsgeschädigter Hornhaut mit Trübungen Vaskularisation Defekten oder Fehlen der Grenzmembranen oder sogar Ersatz der Hornhaut durch sklera ähnliches Gewebe werden kataraktös veränderte oder zerfallene zum Teil abnorm grosse und verlagerte Linsen *(Siemens)* beobachtet Weiterhin können Pseudogliombildung Persistenz des hyaloiden Gefässystems und seiner Hüllen sowie der Tunica vasculosa lentis mangelhafte Glaskörperausbildung schwere Anomalien im Aufbau der Netzhautschichten mit Rosettenbildung Anomalien der Papillenform Netzhautfaltenbildung und Aplasie des N opticus gefunden werden Dazu gehören ebenfalls Fehlbildungen der Iris und des Ziliarkörpers

Der M kann mit zusätzlichen *Missbildungen* des Körpers zum Teil in regelmässig wiederkehrender *syndromaler Form* auftreten 1957 fügte *Meyer-Schwickerath* gemeinsam mit *Gruterich* und *Weyers* den 2 von*Lohmann* in der Literatur beschriebenen Fällen 2 weitere Beobachtungen einer Dysplasia oculo dento digitalis hinzu Es handelt sich um ein Ektodermalsyndrom das einher geht mit Augenveränderungen in Form von M Glaukomneigung und Irisanomalien sowie Schmelzdefekten und Gelbfärbung der Zähne Syndaktylie von Ring und Kleinfinger Kamptodaktylie und A oder Hypoplasie der Mesophalangen ? 5

Die Patienten zeichnen sich weiter aus durch eine eigentümliche Physiognomie mit Pseudohypertelorismus aufwärts gerichteten Nasenöffnungen betontem Nasensteg und eingefallener Mundpartie

Ein ähnliches teratogenetisches Prinzip liegt aller Wahrscheinlichkeit nach einem zweiten Missbildungssyndrom der Dyscranio pygo phalangie *(Ullrich)* zugrunde wobei sich im Gegensatz zu dem ersteren *keine lebensfähigen Probanden* finden Neben einer Zephalozele treten hier schwere Schädel Wirbelsäulen und Extremitätenmissbildungen auf sowie Leistenhoden Hodenhypoplasie und Fehlbildungen an inneren Organen. *Einen ausführlichen histologischen Befund eines mikrophthalmischen Auges* bei dem genannten Syndrom gab *Ballke* 1954 Die Ursache dieser frühembryonal einsetzenden ektodermalen Hemmungsmissbildungen ist beim Menschen noch nicht bekannt. Da bisher Hinweise für eine Vererbung fehlen nimmt man eine exogen embryopathische Schädigung des Feten über die Mutter an die bei beiden Syndromen zur gleichen Zeit aber verschieden stark einsetzen soll *Weyers* (1959) vermutet eine Virusätiologie da die histologischen Besonderheiten der Innenohrepithe

Aus der Universitäts Augenklinik Jena
(Direktor Prof Dr med A Heydenreich)

BEITRAG ZUR HÄUFIGKEIT ERSCHEINUNGSFORM UND ÄTIOLOGIE DES MIKROPHTHALMUS (M)

VON

E HAUSCHILD

Der angeborene M ist eine der häufigsten Missbildungen des Auges Entsprechend den embryonalen Entwicklungsstufen ist eine Einteilung in folgende Gruppen möglich (*Waardenburg van Duyse* zit nach *Badtke* 1961 *von Hippel Seefelder Franceschetti*)

1 reiner M
2 M als extreme Variante von Kolobommissbildungen mit oder ohne Bulbuszyste
3 M ohne Kolobom mit anderen Bulbusanomalien
4 M als Teilsymptom grosser Syndrome

Der ein oder doppelseitig auftretende *reine* M stellt eine graduell unterschiedlich auftretende Hemmungsmissbildung mit einem in allen Teilen harmonisch verkleinerten Bulbus dar Weitere Anzeichen von Missbildungen am Auge fehlen dabei In der Mehrzahl der Falle sehen wir Hyperopie bis zu 25 dptr und einen oft abnorm verkleinerten Hornhautradius Nur in seltenen Fällen findet sich ein myopischer Langbau Die Macula lutea besitzt anatomisch die Unreife eines Neugeborenenauges wodurch die Sehschärfe stark oft bis zur Amaurose herabgesetzt ist Nur ausnahmsweise wird ein ausreichender Visus beobachtet Nystagmus konkomittierendes Einwärtsschielen und Glaukomneigung sowie angeborener Schwachsinn konnen den reinen M begleiten In verschiedenen Graden auftretend bildet er im Extremfall als Bulbusrudiment den Übergang zum Anophthalmus congenitus Von einem inkompletten Anophthal

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Eingegangen am 4 Februar 1969

Spaltbildung ist nach *Franceschetti* die rezessive Vererbung haufiger Hier wurde abwechselndes Auftreten mit Anophthalmus beobachtet Aus der Literatur sind weiterhin geschlechtsgebundene und korrelative Vererbung von M und Cataracta congenita in aufeinanderfolgenden Generationen bekannt Gehaufte Kindersterblichkeit spricht fur das Vorliegen von Letalfaktoren

Nach *Leuenberger* sind Augenmissbildungen haufiger exogenen Einflussen in der Graviditat als Vererbungsfaktoren zuzuschreiben Als exogen bedingt gilt auch der M der bei der retrolentalen Fibroplasie der Fruhgeborenen auftritt, die mit Sauerstoff behandelt wurden Die haufigsten Ursachen aber sind Embryopathien durch Infektion des mutterlichen Organismus im ersten Drittel der Graviditat Unter den Virusinfektionen spielen die Roteln der Mutter die gro ste Rolle Es kommt dabei zu M Katarakt Mikrophakie Glaukom z T auch Megalophthalmus neben weiteren Missbildungen anderer Organe Die nach neueren Ergebnissen zu jeder Zeit der Graviditat mogliche Infektion des Kindes mit Toxoplasmose *(Kraubig* und *Friedberg)* kann zur Embryopathia toxoplasmotica mit Hirn und Augenmissbildungen – darunter M – fuhren

Die intrauterine Augenentzundung wurde in der Vergangenheit als Ursache von Augenhemmungsmissbildungen uberschatzt *(von Hippel Seefelder)* Nur sehr selten kommen echte Falle von angeborener Phthisis bulbi auf Grund fetaler Eiterungen und Entzundungen zur Beobachtung Sie zeichnen sich durch unregelmassige Gestalt des Bulbus narbige Einziehung der Sklera und histologisch gesicherten Entzundungsfolgen aus Kommen die Augen erst im spateren Lebensalter zur Untersuchung so lasst sich schwer beweisen ob die Entzundung Ursache des M ist oder die Entzundung erst spater in dem fur Entzundung disponierten mikrophthalmischen Bulbus *(Heydenreich)* auftrat Auch das Vorliegen von vorderen und hinteren Synechien bei sonst harmonisch gebautem Bulbus ist kein eindeutiger Beweis fur das Vorliegen einer entzundlich bedingten Verkleinerung des Auges Ein Grossteil der hinteren Synechien ist eine Entwicklungsstorung im Zusammenhang mit Aus und Ruckbildung der Pupillarmembran und der Entwicklung der Linse Die vorderen Synechien vor allem di peripher gelegenen konnen dem Missbildungskomplex Rieger Dysgenesis mesodermalis iridis et corneae angehoren einer Entwicklungsstorung der mesodermalen Organe des Vorderabschnittes des Auges

In der Universitats Augenklinik Jena wurde in dem Zeitraum von 1959 bis 19 in 0,15% aller stationaren Aufnahmen (31 von 20579 Patienten) ein M beobachtet Bei der Verteilung auf die Geschlechter uberwiegte das weibliche mit 18 gegenuber dem mannlichen mit 13 Patienten. Darunter waren 6 Sauglinge unter 1 Jahr Kleinkinder zwischen 1 und 2 Jahren 3 Kinder zwischen und 10 Jahren und 15 Patienten im Alter von 10 bis 41 Jahren In 21 Fallen trat der M einseitig auf (11mal rechts 10mal linksseitig) in 10 doppelseitig Mit der Verkleinerung des Auges ging in 10 Fallen gleichzeitig ein Strabismus convergens in 10 weiteren ein Nystagmus in 7 ein Glaukom und in 3

lien denen bei der Rötelnembryopathie vergleichbar sind Nach *Tum* ist je doch auch eine genische Ursache in Form einer Spontanmutation nicht ausge schlossen 1934 machte *von Hippel* auf die engen Beziehungen zwischen Miss bildungen am Auge Gehirn Schädel Extremitaten und den inneren Organen in den allerverschiedensten Kombinationsmöglichkeiten anhand einer vollstan digen Aufzählung der in der Literatur bekannten Fälle unter Hinzufugen eige ner Beobachtungen aufmerksam Er beschrieb u a das gleichzeitige Auftreten von M bzw Bulbuszysten und dem Lindau schen Symptomenkomplex sowie der Angiomatosis retinae ferner die Kombination mit Mikrozephalie Idiotie und Taubheit Über Mikrophthalmie bei Mikrozephalie berichtete bereits *Pflu ger* 1885

Sjögren und *Larsson* (zit nach *Leuenberger*) beschrieben 1949 das Syndrom *Mikro oder Anophthalmus und Oligophrenie in Schweden Das gekoppelte* Auftreten von M Cataracta congenita Papageienschnabelnase Mikrognathie Zahnstellungsanomalien und Hypotrichose ist als Hallermann Streiff Syndrom bekannt Unter dem sogenannten Patau Syndrom (zit nach *Heimann*) verstehen wir Augenmissbildungen darunter M Kolobombildungen der Uvea und Dys plasia retinae denen ursächlich eine Trisomie eines Autosomes der Gruppe D 15 zugrunde liegt

Über das syndromale erbliche *Auftreten von M und Arhinenzephalie* be richtete *Badtke* 1948 ausfuhrlich Aus der Literatur konnte er weitere Beobach tungen von Kombinationen des M mit familiärem Zwergwuchs Atresie der Tränennasengange Missbildungen am Herzen und der grossen Gefässe hin u fügen *P Hermann* beschrieb erstmalig das Syndrom M Retinitis pigmentosa und Glaukom *Gagianut* und *Schmid* sehen in der *Kombination M Iris* und Aderhautkolobome und Analatresie eine neue Chromosomenkrankheit

Wie experimentelle Untersuchungen eindeutig ergaben ist die normale Bul busentwicklung abhängig von einer regelrechten Netzhautentwicklung und der gestaltbildenden Kraft der Linse Kommt es durch genisch erbliche Faktoren oder durch exogene Einflusse zu einer Storung in der Entwicklung des *inneren* Augenbecherblattes insbesondere der Netzhaut so resultiert ein M in den ver schiedensten Typen und Ausprägungsgraden Im Einzelfall ist die alternative Entscheidung in der Frage der kausalen Genese des M oft nicht zu treffen da Erblichkeit nicht nachgewiesen werden kann oder sichere pathogene aussere Einflusse nicht zu ermitteln sind Auch an das Zusammentreffen von erblichen und exogenen Faktoren muss gedacht werden

Es *gibt zahlreiche* Stammbäume welche die erbliche Genese des M beweisen Beim reinen M ist ein recessives oder dominantes Verhalten des Erbganges nicht eindeutig gesichert während bei gleichzeitiger Kolobombildung die do minante Vererbung vorherrscht In gleichen Familien wurde die *Kombination* M mit Kolobombildung an einem und Anophthalmus am anderen Auge sowie M *einerseits und* Kolobombildung am zweiten Auge beobachtet Beim M ohne

Myopie und Hyperopie fanden sich eine Myopia alta bei 2 und eine hohe Hyperopie bei 3 Patienten

Die Sehschärfe war jedoch in fast allen Fällen bis auf 5/25 partim und mehr herabgesetzt Daneben bestanden 6mal Amaurose und 4mal fehlende Fixation Bei einem Patienten mit auffälligem M congenitus beiderseits der rechts stärker ausgeprägt war als links und gleichzeitigem Papillen und Aderhautkolobom sowie einem Engwinkelglaukom beobachteten wir einen Visus rechts von Fingerzählen vor dem Auge und links na h Korrektur eines geringen Astigmatismus mixtus das nur sehr selten zu verzeichnende Sehvermögen von 5/10 partim

Entsprechend obiger Einteilung bestand nur in 2 Fällen ein reiner M ohne andere Augenanomalien

In 18 Fällen lag ein *M ohne Spaltbildungen* aber *mit anderen Augenmissbildungen* vor Eine begleitende Cataracta congenita fand sich 10mal (Beispiel s Abb 1) davon ? bei Rötelnembryopathie Ein beiderseitiger M mit Schichtstar wies noch eine Optikusatrophie links auf ein weiterer ein Leucoma corneae mit oberflächlicher und tiefer Vaskularisation und bandförmiger Hornhautdegeneration Im letzteren Fall wurden bei der Extractio lentis erhebliche Glaskörperveränderungen wahrscheinlich Reste eines Abszesses nachgewiesen Der histologische Befund des mit der Linse verbundenen Gewebskonglomerates ergab neben Kapselresten Pigmentgewebsanhäufungen und einem Fibrocytengeflecht lockere Netzhautanteile mit Rosettenbildung Die zweireihige Körnerschicht war nur teilweise erhalten und stark dysplastisch verändert

In 4 Mikrophthalmusfällen bestand eine gleichzeitige Pseudogliombildung Während in 1 Falle die Ätiologie des Pseudoglioms ungeklärt blieb lag die Ursache einmal in einer Toxoplasmose einmal in einer Hyperplasie des primären Glaskörpers (s Abb ?) bei einem anderen Fall in einer frühkindlichen Infektion des Auges mit zunehmender Synechierung der Iris und fortschreitender Linsentrübung die vom 4 bis 8 Lebensmonat von uns verfolgt wurden Kinderklinisch konnten hierbei Ausgangsherde die für eine metastatische Enophthalmitis in Frage kommen konnten ausgeschlossen werden

Weiterhin wurden Mikrophthalmi mit echter Nebenpupille sowie mit einer Optikusatrophie neben Ablatio retinae beobachtet Ausserdem sahen wir 2 Bulbusrudimente die der prothetischen Versorgung bedurften Es handelte sich dabei einmal um die Folgen einer Zangengeburt wobei sich n ben einer Ptosis ein Bulbusrudiment mit einer durch skleraähnliches Gewebe ersetzten Hornhaut fand Die Bewegung des Bulbus war dabei erhalten In dem anderen Fall lag eine Mikroorbita mit Mikrobulbus Mikrokornea und Blepharophimose vor wobei zum Einlegen einer Augenprothese eine operative Lidspaltenerweiterung durchgeführt wurde

? Mikrophthalmi zeigten *Kolobombildung und andere Augenveränderungen* Unter diesen waren ein beiderseitiger M mit atypischem nach nasal verlaufen

ein Strabismus divergens einher. Bei 1 Kinde bestand eine Parese des Musculus rectus superior, das Auge konnte nicht über die Mittellinie nach oben bewegt werden.

Bei 2 Patienten wurde der M. erst im Alter von 6 bis 9 Jahren anhand einer Sehverschlechterung bemerkt. Bei den anderen Kindern wurden die Eltern unmittelbar nach der Geburt oder in den folgenden Monaten darauf aufmerksam.

Bei den von uns beobachteten und zum Teil kürzlich nachuntersuchten Fällen von M. sahen wir die unterschiedlichsten Grade und die mannigfaltigsten *Typen entsprechend dem oben beschriebenen Einteilungsschema. Einen kurzen* Überblick gibt die Tabelle.

Eine subjektive Refraktionsbestimmung war häufig auf Grund des Alters der Kinder, eine objektive wegen Medientrübungen nicht möglich. Neben geringer

Übersichts-Tabelle

	Anzahl
Mikrophthalmus	31
Frauen	18
Männer	13
einseitig (11mal rechts, 10mal links)	21
doppelseitig	10
Mikrophthalmus und Strabismus convergens	10
Mikrophthalmus und Strabismus divergens	3
Mikrophthalmus und Nystagmus	10
Mikrophthalmus und Glaukom	7
Mikrophthalmus und Parese des Musculus rectus superior	1
reiner Mikrophthalmus	2
Mikrophthalmus ohne Spaltbildungen, aber anderen Augenanomalien	18
Mikrophthalmus mit Spaltbildungen und anderen Augenfehlbildungen	6
Mikrophthalmus mit Missbildungen des Körpers	5
Ätiologie	
ungeklärt	18
Embryopathie	7
intrauterine Infektion	1
Zangengeburt	1
erblich	4

dem Aderhaut und Papillenkolobom unter Einschluss der Makula rechts und spiegelbildlich nach nasal gelegenem Aderhautkolobom links und ein weiterer doppelseitiger M mit Papillenkolobom und spiegelbildlicher nach temporal unten zum Ziliarkorper und der Linsenhinterwand verlaufender und gefässführender Ablatio falciformis congenita beiderseits In 2 Fallen fand sich ein typisches Iriskolobom einmal kombiniert mit einer Pseudogliombildung bei Toxoplasmose und einem talergrossen Haemangiom der Wange Ausserdem gelangte ein nach temporal oben gelegenes atypisches Aderhautkolobom zur Beobachtung Bei einem Saugling traf ein typisch nach unten gelegenes Aderhautkolobom am rechten Auge mit einem atypischen nasal der Papille gelegenen am linken Auge zusammen *Badtke* berichtete ebenfalls von dieser sehr seltenen Kombination und glaubte das atypische Kolobom am ehesten durch eine atypische Lage der Becherspalte erklaren zu konnen

In der Gruppe des *M mit Missbildungen des Korpers* beobachteten wir das Auftreten einer Cheilognathopalatoschisis bei einer Retinitis proliferans rechts und einem M mit Cataracta congenita links auf Grund einer Toxoplasmose

Ein Patient mit M und persistierender Arteria hyaloidea wies Pseudoepiphysenbildungen der Metacarpalia 2 5 beiderseits auf

Begleitenden Epikanthus sahen wir zweimal einmal bei beiderseitigem partiellen Papillenkolobom ein anderes Mal bei atypischem Kolobom nach temporal auf der einen Seite und Anophthalmus ohne nachweisbaren Bulbusrest auf der anderen

Bei einer 46jahrigen Patientin und deren ambulant untersuchten 21jahrigen Tochter konnten wir ein interessantes Krankheitsbild mit Zusammentreffen von M und anderen Korpermissbildungen in syndromaler Form beobachten Die Mutter wies neben einem beiderseitigen M mit hoher Hyperopie und Glaukom Schmelzdefekte der Zahne Klinodaktylie des Kleinfingers seit Geburt bestehende Schwerhorigkeit und eine charakteristisch veranderte Nase auf die sich durch einen verbreiterten Rucken eine breite und abgeplattete Spitze verkurzten Steg und relativ klein angelegte Nasenlocher auszeichnete Nasenveranderungen in typisch ahnlicher Weise zeigte die Tochter (s Abb 3 4 5) *) Die Missbildungen der Mutter wenn man von der vorliegenden Schwerhorigkeit absieht konnten in das von *Meyer Schwickerath Gruterich* und *Weyers* beschriebene Syndrom der Dysplasia oculo dento digitalis eingeordnet werden Wegen der zusatzlichen Schwerhorigkeit die bei der Tochter audiographisch als ein Defekt des Mittelohres (Schalleitungsstorung) geklart werden konnte ist jedoch an das Vorliegen eines eigenen selbstandigen Syndroms zu denken Bei der Tochter bestehen ebenfalls M und hohe Hyperopie Zahn und Extremitatenuntersuchungen wurden leider nicht durchgefuhrt Aufforderungen zur

*) Frau Prof R Albrecht Direktor der Universitats HNO Klinik Jena danke ich recht herzlich fur das freundliche Uberlassen der Befunde von Fraulein H T

Abb 1
Mikrophthalmus mit Cataracta congenita links



Abb 2
Mikrophthalmus links mit partieller sektorenförmiger Linsentrübung zwischen 9 und 12 Uhr und Pseudogliombildung auf Grund einer *Hyperplasie* des primären *Glaskörpers*

dem Aderhaut und Papillenkolobom unter Einschluss der Makula rechts und spiegelbildlich nach nasal gelegenem Aderhautkolobom links und ein weiterer doppelseitiger M mit Papillenkolobom und spiegelbildlicher nach temporal unten zum Ziliarkorper und der Linsenhinterwand verlaufender und gefäss führender Ablatio falciformis congenita beiderseits In 2 Fällen fand sich ein typisches Iriskolobom einmal kombiniert mit einer Pseudogliombildung bei Toxoplasmose und einem talergrossen Haemangiom der Wange Ausserdem gelangte ein nach temporal oben gelegenes atypisches Aderhautkolobom zur Beobachtung Bei einem Säugling traf ein typisch nach unten gelegenes Aderhautkolobom am rechten Auge mit einem atypischen nasal der Papille gelegenen am linken Auge zusammen *Badtke* berichtete ebenfalls von dieser sehr seltenen Kombination und glaubte das atypische Kolobom am ehesten durch eine atypische Lage der Becherspalte erklaren zu können

In der Gruppe des M *mit Missbildungen des Körpers* beobachteten wir das Auftreten einer Cheilognathopalatoschisis bei einer Retinitis proliferans rechts und einem M mit Cataracta congenita links auf Grund einer Toxoplasmose

Ein Patient mit M und persistierender Arteria hyaloidea wies Pseudoepiphysenbildungen der Metacarpalia 2 5 beiderseits auf

Begleitenden Epikanthus sahen wir zweimal einmal bei beiderseitigem partiellen Papillenkolobom ein anderes Mal bei atypischem Kolobom nach temporal auf der einen Seite und Anophthalmus ohne nachweisbaren Bulbusrest auf der anderen.

Bei einer 46jährigen Patientin und deren ambulant untersuchten 21jährigen Tochter konnten wir ein interessantes Krankheitsbild mit Zusammentreffen von M und anderen Körpermissbildungen in syndromaler Form beobachten Die Mutter wies neben einem beiderseitigen M mit hoher Hyperopie und Glaukom Schmelzdefekte der Zähne Klinodaktylie des Kleinfingers seit Geburt bestehende Schwerhörigkeit und eine charakteristisch veränderte Nase auf die sich durch einen verbreiterten Rücken eine breite und abgeplattete Spitze verkürzten Steg und relativ klein angelegte Nasenlöcher auszeichnete Nasenveränderungen in typisch ähnlicher Weise zeigte die Tochter (s Abb 3 4 5) *) Die Missbildungen der Mutter wenn man von der vorliegenden Schwerhörigkeit absieht konnten in das von *Meyer Schwickerath Gruterich* und *Weyers* beschriebene Syndrom der Dysplasia oculo dento digitalis eingeordnet werden Wegen der zusätzlichen Schwerhörigkeit die bei der Tochter audiographisch als ein Defekt des Mittelohres (Schalleitungsstörung) geklärt werden konnte ist jedoch an das Vorliegen eines eigenen selbständigen Syndroms zu denken Bei der Tochter bestehen ebenfalls M und hohe Hyperopie Zahn und Extremitätenuntersuchungen wurden leider nicht durchgeführt Aufforderungen zur

*) Frau Prof R Albrecht Direktor der Universitäts HNO Klinik Jena danke ich recht herzlich für das freundliche Überlassen der Befunde von Fräulein H T



Abb 3 4 5
Syndromales Auftreten von charakteristischen Nasenveranderungen und Mikrophthalmus (s Text)

Nachuntersuchung auch an weitere Familienmitglieder mutterlicherseits die nach der Anamnese ebenfalls Missbildungen aufweisen sollen blieben unbeantwortet

Bei dem Versuch der Klärung der Atiologie des M konnte in mehreren Fallen weder ein Anhalt fur ein erbliches Auftreten noch für das Wirken exogen embryopathischer Noxen gefunden werden Bei 18 Patienten blieb die Ursache ungeklart In 6 Fallen lag den Hemmungsmissbildungen des Auges sicher in 1 Fall wahrscheinlich eine Embryopathie zugrunde (4mal Toxoplasmose 2mal Rubeolen 1 grippaler Infekt im dritten Schwangerschaftsmonat) Eine intrauterine Augenentzundung wurde auf Grund von Überresten eines Glaskorperabszesses als kausale Genese angenommen Ein mit Ptosis kombinierter M war auf Schadigung bei Zangengeburt zuruckzufuhren Über einen Fall von manglhaftem Bulbuswachstum nach Geburtszangenverletzung des Sehnerven berichtete ebenfalls *Vogt* (zit n *Badtke*) Auch im Tierversuch (*Hertel* zit n *Badtke*) konnte bereits durch Durchtrennung des Sehnerven vor Eintritt in den Bulbus unter Schonung des Netzhautkreislaufes und der hinteren Ziliargefasse beim Kaninchen ein harmonisch geformter reiner M erzeugt werden

In 4 Fallen lasst sich eine erbliche Genese nachweisen Eine 27jahrige Patientin stand wegen angeborenem M beiderseits mit Schichtstar Nystagmus und Optikusatrophie links in unserer Behandlung Bei einer Visusherabsetzung auf Handbewegung dicht vor dem Auge rechts und intakter Lichtscheinprojektion links wuchs die Patientin in einer Blindenschule auf wie zuvor ihre Mutter die ebenfalls einen beiderseitigen M mit Schichtstar hatte Eine 66jahrige Patientin die wegen einer Astvenenthrombose links bei M rechts mit Cataracta

congenita in unserer stationaren Behandlung stand berichtete anamnestisch von einem angeborenen Linsenschaden ihres Sohnes

Bei der Nachuntersu hung einer 26jahrigen Patientin mit beiderseitigem M und Cataracta congenita grobschlagigem rotatorischen Nystagmus und Glau kom stellte diese uns ihre 2jahrige Tochter vor die ebenfalls einen M zeigte Die Untersuchung ergab folgenden Befund

M mit Cataracta congenita beiderseits und Strabismus convergens ex anop sia rechts Keine Visusangaben Hornhautdurchmesser rechts 9 0 links 9 5 mm Linse rechts vorderer Polstar mit Zentralstar links massiger Zentralstar Fun dus b iderseits soweit einsehbar frei von pathologischen Veranderungen Ten sion beiderseits *5 0/5 5* = 17 mm Hg

Fine eindeutige erbliche Genese liegt auch bei den Krankheitsformen von Mutter und Tochter vor die sich durch einen syndromalen Charakter aus zeichnen und uber die bereits oben berichtet wurde

Zusammenfassung

Nach einem kurzen Überblick uber das Wesen des M anhand des Schrifttums wird uber 31 Patienten der Universitats Augenklinik Jena berichtet die in der Zeit von 1958 bis 1967 wegen eines M stationar behandelt wurden Neben ei ner Gruppierung in reinen M M mit und ohne Spaltbildungen aber anderen Augenanomalien und M mit zusatzlichen Korpermissbildungen wird weiterhin auf atiologische Momente eingegangen Im Grossteil der Falle kann ein sicherer Anhalt fur die kausale Genese nicht erbracht werden 6mal liegt den Hem mungsmissbildungen des Auges sicher 1mal wahrscheinlich eine Embryopathie 1mal eine intrauterine Infektion und zum anderen Folgen einer Zangengeburt zugrunde In 4 Fallen liegt eine erbliche Gene e vor

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Abb. 3, 4, 5
Syndromales Auftreten von charakteristischen Nasenveränderungen und Mikrophthalmus (s. Text)

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From the Steno Memorial Hospital (Niels Steensens hospital) Gentofte Denmark (Chief Jac E Poulsen) and the Ophthalmic Pathology Laboratory Rigshospitalet Copenhagen Denmark (Chief S Ry Andersen)

IMMUNOHISTOLOGICAL STUDIES ON HUMAN DIABETIC AND NON DIABETIC EYES

I Fluorescent labelling of insulin and insulin antibodies

BY

A U WERNER and H W LARSEN

The possible role of insulin antibodies in the development of diabetic angiopathy has been discussed during recent years (*Berns Blumenthal et al* 1962 1963 and 1964)

Coleman et al (1962) applied insulin labelled with fluorochrome to human diabetic eyes and in eyes with diabetic retinopathy found fluorescent insulin to be bound specifically to the retinal capillary aneurysms and to the basement membranes of the retinal epithelia in ciliary body and iris The authors however did not mention anything about changes in the vessels of the iris ciliary body and choroid or in vascular proliferations

In order to evaluate insulin and insulin antibody binding reactions in tissue diabetic and non diabetic eyes were investigated by immunofluorescent and autoradiographic tracing

This paper will deal with the former techniques and a second paper with the latter techniques

Material and Methods

The material consisted of 14 non diabetic eyes and 30 diabetic eyes with retinopathy The non diabetic group consisted of 8 men and 6 women the dia

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betic group of 16 men and 14 women The mean age was 50 (1 84) in non diabetics and 53 in diabetics (25 85) Duration of diabetes was from 7 55 years mean 22 years 8 of the patients were diabetic for 25 years or more The specimens investigated were obtained at autopsy or after enucleation

The following methods were employed

Conjugates of fluorescein isothiocyanate (FITC) were used according to the method of *Werner* (1968a) Pure pig insulin and an immunoglobulin (IgG) fraction of diabetic and non diabetic sera were used for conjugation with FITC Purification procedures were performed using column chromatography Sephadex G 25

The fluorescein protein ratio for insulin was 1 07 1 (monosubstitution) for the IgG fraction of sera 2 7 1 Electrophoretic and spectrophotometric controls of conjugate properties were made in each case

Incubation assays of formalin fixed paraffin embedded serial sections The sections were incubated with FITC insulin in a concentration of 150 micro units/ml incubating medium (1 microunit = 0 04 × 10^{-6} mg insulin incubating medium = 0 01 molar phosphate buffer pH 7 1) Incubation took place in a closed chamber of constant humidity for a period of 30 minutes

Details of the procedures using labelled fractions of sera are described in the above mentioned paper

The sections were examined for the following features

1) Autofluorescence

2) FITC conjugated insulin incubation

3) Preincubation with unlabelled insulin to control 2)

4) Incubation with an FITC tagged immunoglobulin IgG fraction of diabetic sera (pool and single) indirect technique

5) Incubation with immunoglobulin fractions of non diabetic sera labelled with FITC to control 4) indirect technique

To increase the reliability of the methods the immunohistological techniques were standardized in order to secure reproducible experiments to obtain con sistent results and to ensure fewer possibilities of introducing artefactual reac tions (*Werner* 1968a)

Results

The results were evaluated by comparing colour photographs of sections with the same time of exposure and identical exciter and ocular filter equipment Anscochrome daylight film 200 ASA was used The large fluorescence micro

scope (Carl Zeiss Western Germany) with illumination provided by an HBO 200 Watt mercury lamp was employed

The results are shown in Figs 1 27 and listed in Table 1 The intensity of fluorescence is arbitrarily graded in steps from 0 to 5

Autofluorescence

The autofluorescence observed in the eye tissues examined was zero or minimal (grade 0 to 1) and therefore did not interfere with any of the fluorescent reactions mentioned below

Incubation with FITC-conjugated insulin

Cornea

In diabetic eyes Bowman s membrane stroma and Descemet s membrane showed a moderate degree (grade 2) of fluorescence while there was no fluorescence in the epithelium and endothelium

In non diabetic eyes there was a minimal (grade 1) fluorescence of the same three structures

Ciliary body

In diabetic eyes there was heavy fluorescence (grade 3) of the unpigmented ciliary epithelium stroma and vessel walls and very heavy fluorescence of the basement membrane of the ciliary processes (grade 4) and the endothelial lining and basement membrane of the vessels (grade 4) whereas the pigment epithelium did not show any fluorescence

In non diabetic eyes minimal (grade 1) fluorescence of endothelial lining and basement membrane of vessel walls was observed Fluorescence (grade 1) of the stroma was occasionally seen in eyes from aged persons No other structures presented fluorescence

Iris

In diabetic eyes fluorescence was observed in the basement membrane of the pigment epithelium and/or dilator muscle of the iris (grade 4) in the stroma (grade 1) in the endothelial lining and basement membranes (grade 4) and in the vessel wall (grade 3) while the pigment epithelium showed no fluorescence

In cases where the pigment epithelium was vacuolated and presented a lacy appearance a moderate degree of fluorescence was observed (grade 2)

Non diabetic eyes presented slight fluorescence of the basement membrane of the iris (grade 1)

In the vessels there was minimal fluorescence grade (1) of basement membranes and endothelial lining but otherwise no fluorescence

Fig 1 Ciliary processes from a non diabetic patient aged 70 years Although there is binding to connective tissue fibers in some of the processes fluorescence of the vessel walls endothelial lining and basement membranes is absent
FITC conjugated insulin Magnification × 60 Lab No 6 67

Fig 2 Same ciliary processes as in fig 1 Practically no fluorescence is discernible
The preparation has been preincubated with insulin. Magnification × 60 Lab No 6 6

Fig 3 The same structures shown in figs 1 and 2
This section has been treated with labelled diabetic serum (indirect technique) and displays no definite degree of fluorescence Magnification × 60 Lab No 6 67

Fig 4 Ciliary processes from a diabetic illustrating fluorescence due to insulin fluorescein isothiocyanate binding Heavily stained endothelial lining and basement membranes and marked colouring of the vessel walls could be seen
Magnification × 60 Lab No 3?5 60

Fig 5 Ciliary processes from the same eye as fig 4
This section illustrates the reduction of fluorescent binding caused by prior incubation with insulin
Magnification × 60 Lab No 355 60

Fig 6 Section of ciliary processes from a diabetic eye
Indirect staining technique using incubation with labelled diabetic serum A much higher degree of fluorescence is elicited here than in the ciliary processes in the non diabetic eye shown in fig 3 (× 60) Lab No 26? 62

Fig 7 Closer view of ciliary processes from a normal aged person
Some FITC insulin binding to stromal fibers is noted but no fluorescence as far as the basement membrane of the processes and the vessels are concerned
Magnification × 150 Lab No 565 66

Fig 8 Ciliary processes from a diabetic The basement membrane of the processes and the vessels are brightly fluorescing
FITC insulin incubation (× 150) Lab No 4/6 62


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Fig 4 Ciliary processes from a diabetic illustrating fluorescence due to insulin fluorescein isothiocyanate binding Heavily stained endothelial lining and basement membranes and marked colouring of the vessel walls could be seen
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Magnification × 150 Lab No 365/66

Fig 8 Ciliary processes from a diabetic The basement membrane of the processes and the vessels are brightly fluorescing
FITC insulin incubation (× 150) Lab No 476/62


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Fig 9 High magnification (× 600) of a ciliary process from a diabetic eye Marked fluorescence of the neuroepithelium and basement membrane of the process and of the structures in the vessels due to FITC insulin binding Lab No 335/60

Fig 10 Same ciliary process as in fig 9 There is an attenuation of fluorescence caused by binding of non conjugated insulin to the tissue – thereby blocking the attachment sites of FITC insulin Incubation with insulin followed by exposure to FITC insulin Magnification × 600 Lab No 335/60

Fig 11 Ciliary process from a diabetic eye The broad basement membrane of the process exhibits a net like appearance and shows an ultimate degree of fluorescence Some lymphocytes are present – also highly fluorescing
FITC insulin Magnification × 600 Lab No 335/60

Fig 12 Same view as fig 11 Diminution of fluorescence caused by previous incubation with unlabelled insulin
Magnification × 600 Lab No 335/60

Fig 13 Part of the iris from a non diabetic patient aged [illegible]0 years Practically no binding of FITC insulin to basement membranes of the iris and vessels occurred
Magnification × 60 Lab No 6/67

Fig 14 Part of the iris from a 48 year old diabetic
Pronounced binding to basement membranes of the iris and vessels could be noted
FITC insulin Magnification × 60 Lab No 335/60

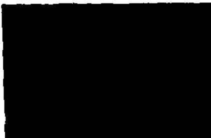
Fig 15 Vessels of the iris from an aged non diabetic person
Lamellar thickened appearance of vessel walls in the loose connective tissue – but only slight FITC insulin fluorescent binding
Magnification × 600 Lab No [illegible]6[illegible]

Fig 16 Iris vessel from a 40 year old diabetic Perivascular fluorescence and marked condensation and augmentation of the vessel wall Endothelial lining and basement membrane are highly fluorescent
FITC insulin treated section (× 600) Lab No 4/6/62


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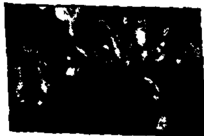

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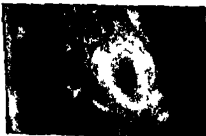

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Fig 9 High magnification (× 600) of a ciliary process from a diabetic eye Marked fluorescence of the neuroepithelium and basement membrane of the process and of the structures in the vessels due to FITC insulin binding Lab No 335 60

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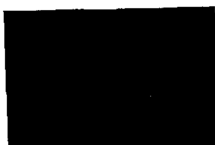
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FITC insulin treated section (× 600) Lab No 476 62


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Fig 17 Detail of the iris from a diabetic 58 years of age
This preparation – incubated with labelled IgG fraction of diabetic serum – displays marked fluorescence of endothelial lining basement membrane and vessel wall
Magnification × 600 Lab No 267 62

Fig 18 The retina choroid and sclera in low magnification (× 60) from a normal person The fluorescence seen in the sclera and Bruch s membrane is partly due to auto fluorescence – partly a result of the preponderance in this region of reticulin and elastic fibers which might have insulin binding properties
FITC insulin (× 60) Lab No 6 67

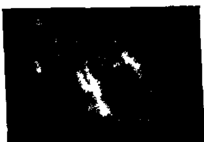
Fig 19 The same structures as in fig 18 but from a diabetic person
There is bright fluorescence of the retinal vessels the choroidal vessels and the sclera
Incubation with FITC conjugated insulin (× 60) Lab No 385 60

Fig 20 The same structures from the same patient as shown in fig 19
The section has been preincubated with insulin before application of FITC insulin The reduction of fluorescence is obvious
Magnification × 60 Lab No 385 60

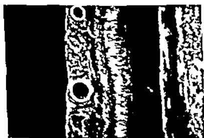
Fig 21 Proliferative diabetic retinopathy
The new formed vessels and connective tissue proliferations present very marked fluorescence
FITC insulin incubated section (× 600) Lab No 596 66

Fig 22 Proliferation in diabetic retinopathy The effect of previous incubation with unlabelled insulin before application of FITC conjugated insulin Distinct quenching of fluorescence is noticed
Magnification × 600 Lab No 76 67

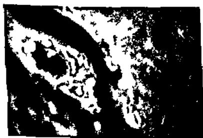
Fig 23 Similar view of proliferative diabetic retinopathy
Incubation assay with diabetic serum conjugated with FITC using an *indirect technique*
Marked fluorescence could be seen (× 600) Lab No 267 62


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Fig 17 Detail of the iris from a diabetic 38 years of age
This preparation – incubated with labelled IgG fraction of diabetic serum – displays marked fluorescence of endothelial lining basement membrane and vessel wall
Magnification X 600 Lab No 26//62

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Fig 22 Proliferation in diabetic retinopathy The effect of previous incubation with unlabelled insulin before application of FITC conjugated insulin Distinct quenching of fluorescence is noticed
Magnification X 600 Lab No 26/ 62

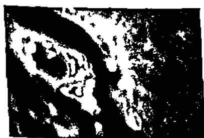
Fig 23 Similar view of proliferative diabetic retinopathy
Incubation assay with diabetic serum conjugated with FITC using an indirect technique
Marked fluorescence could be seen (X 600) Lab No 267/62

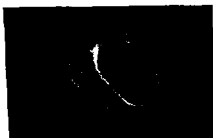

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Fig 17 Detail of the iris from a diabetic 38 years of age
This preparation – incubated with labelled IgG fraction of diabetic serum – displays marked fluorescence of endothelial lining basement membrane and vessel wall
Magnification × 600 Lab No 267/62

Fig 18 The retina choroid and sclera in low magnification (× 60) from a normal person The fluorescence seen in the sclera and Bruch s membrane is partly due to auto fluorescence – *partly a result of the preponderance in this region of reticulin and* elastic fibers which might have insulin binding properties
FITC insulin (× 60) Lab No 6/67

Fig 19 The same structures as in fig 18 but from a diabetic person
There is bright fluorescence of the retinal vessels the choroidal vessels and the sclera
Incubation with FITC conjugated insulin (× 60) Lab No 835/60

Fig 20 The same structures from the same patient as shown in fig 19
The section has been preincubated with insulin before application of FITC insulin The reduction of fluorescence is obvious
Magnification × 60 Lab No 835/60

Fig 21 Proliferative diabetic retinopathy
The new formed vessels and connective tissue proliferations present very marked fluorescence
FITC insulin incubated section (× 600) Lab No 596/66

Fig 22 Proliferation in diabetic retinopathy The effect of previous incubation with unlabelled insulin before application of FITC conjugated insulin Distinct quenching of fluorescence is noticed
Magnification × 600 Lab No 267/62

Fig 23 Similar view of proliferative diabetic retinopathy
Incubation assay with diabetic serum conjugated with FITC using an indirect technique
Marked fluorescence could be seen (× 600) Lab No 267/62


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Fig 24 Retinal pigment epithelium Bruch s membrane and choroid from a non diabetic person
*Pigment epithelium and Bruch s membrane show slight fluorescence None of the ves*sels demonstrated binding reactions with FITC labelled insulin (X 600) Lab No 5/67

Fig 25 The same structures as fig 24 – from a diabetic eye
An FITC insulin treated section
Pigment epithelium *displays some degree of fluorescence* Bruch s membrane and the choroidal vessels are intensely fluorescent Magnification X 600 Lab No 335/60

Fig 26 Single choroidal vessel from a diabetic illustration FITC insulin binding phenomena of the same character (X 600) Lab No 596/66

Fig 27 Choroidal vessel from a diabetic
Incubation with FITC tagged diabetic gamma globulin using a sandwich layer technique Apparent fluorescence is of similar intensity to that demonstrated *in fig 26* (X 600) Lab No 267/62



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Fig 24 Retinal pigment epithelium Bruch s membrane and choroid from a non diabetic person
Pigment epithelium and Bruch s membrane show slight fluorescence None of the vessels demonstrated binding reactions with FITC labelled insulin (× 600) Lab No 5 67

Fig 25 The same structures as fig 24 – from a diabetic eye
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Pigment epithelium displays some degree of fluorescence Bruch s membrane and the choroidal vessels are intensely fluorescent Magnification × 600 Lab No 335/60

Fig 26 Single choroidal vessel from a diabetic illustration FITC insulin binding phenomena of the same character (× 600) Lab No 596/66

Fig 27 Choroidal vessel from a diabetic
Incubation with FITC tagged diabetic gamma globulin using a sandwich layer technique Apparent fluorescence is of similar intensity to that demonstrated in fig 26 (× 600) Lab No 267/62


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Table 1

	Autofluorescence		Incubation with FITC insulin		Preincubation with unlabelled insulin		Diabetic sera – indirect technique	
	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
Cornea								
Epithelium	0	0	0	0	0	0	0	0
Bowman's membrane	1	1	1	2	1	2	2	2
Stroma	0	0	1	2	0	1	1	1
Descemet's membrane	0	0	1	2	0	1	1	1
Endothelium	0	0	0	0	0	0	0	0
Ciliary body								
Neuroepithelium	0	0	0	3	0	(1)	0	3
Pigment epithelium	0	0	0	0	0	0	0	0
Basement membrane	0	0	0	4	0	(1)	0	4
Stroma	0	0	1	3	0	(1)	0	2
Vessels	0	0	1	4	0	(1)	0	4
Endothelial lining and basement membrane								
Vessel walls	0	0	0	3	0	(1)	0	3
Iris								
Stroma	0	0	0	1	0	0	0	1
Basement membrane	0	0	1	4	0	(1)	0	2
Pigment epithelium	0	0	0	0	0	0	0	0
Vessels	0	0	(1)	4	0	1	0	3
Endothelial lining and basement membrane								
Vessel walls	0	0	0	3	0	(1)	0	2

Lens								
Capsule	(1)	(1)	1	1	(1)	(1)	(1)	1
Stroma	(1)	(1)	1	1	(1)	(1)	(1)	1
Retina								
Inner limiting membrane	0	0	0	3	0	0	0	[illegible]
Nerve fiber layer	0	0	0	[illegible]	0	0	0	1
Ganglion cell layer	0	0	0	2	0	0	0	1
Inner plexiform layer	0	0	0	1	0	0	0	(1)
Inner nuclear layer	0	0	0	2	0	0	0	1
Outer plexiform layer	0	0	0	1	0	0	0	(1)
Outer nuclear layer	0	0	0	[illegible]	0	0	0	1
Outher limiting membrane	0	0	0	2	0	0	0	1
Layer of rods and cones	0	0	0	1	0	0	0	0
Pigment epithelium	0	0	(1)	2	0	0	(1)	1
Vessels								
Endothelial lining and basement membrane	0	0	0	4	0	1	0	4
Vessel walls	0	0	0	4	0	1	0	4
Proliferative diabetic lesions								
New formed vessels								
Endothelial lining and basement membrane	–	0	–	[illegible]	–	1	–	[illegible]
Vessel walls	–	0	–	5	–	1	–	5
Connective tissue proliferation	–	0	–	4	–	(1)	–	3
Bruch's membrane	(1)	(1)	1	3	(1)	(1)	(1)	[illegible]

Table 1 (cont.)

	Autofluorescence		Incubation with FITC insulin		Preincubation with unlabelled insulin		Diabetic sera – indirect technique	
	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
Choroid								
Stroma	0	0	0	1	0	0	0	(1)
Vessels								
Endothelial lining and basement membrane	0	0	0	4	0	1	0	3
Vessel walls	0	0	0	4	0	1	0	3
Sclera								
Stroma	0	0	1	2	(1)	1	(1)	1
Optic disc and nerve								
Vessels								
Endothelial lining and basement membrane	0	0	0	4	0	1	0	4
Vessel walls	0	0	0	4	0	1	0	4

Lens
Diabetic as well as non diabetic eyes showed grade 1 fluorescence with no difference between the capsule and the stroma

Retina
Diabetic eyes The endothelial lining basement membranes and vessel walls showed grade 4 of fluorescence intensity and the internal limiting membrane showed grade 3 while the fluorescence of remaining structures varied from grade 1 2

Non diabetic eyes presented no definite fluorescence

Proliferative diabetic lesions
Neovascularizations showed an ultimate degree (grade 5) of fluorescence and connective tissue proliferations grade 4

Bruch s membrane
In diabetic eyes the membrane of Bruch presented grade 3 of fluorescence while non diabetic eyes showed grade 1

Choroid
Diabetic eyes showed grade 4 of fluorescence in the vessels and grade 1 in the stroma while non diabetic eyes did not present any definite fluorescence

Sclera
In diabetic eyes the sclera presented grade 2 of fluorescence while non diabetic eyes showed grade 1

Optic nerve and retrobulbar fat tissue
In those sections of diabetic eyes in which the optic disc and nerve were present as well as those containing retrobulbar fat the vessels showed the same pattern of fluorescence as in the retina Fat cell membranes also bound insulin (grade 3)

Non diabetic eyes showed no binding

Preincubation with Insulin

Fluorescence could be reduced by previous incubation with unlabelled insulin before exposure of sections to FITC conjugated insulin

The concentration of insulin applied – whether conjugated to FITC or not – was held at 150 microunits/ml phosphate buffer which is within the limits of postprandial plasma insulin values in normals It was possibl to obtain further diminution in residual fluorescence (in practice total quenching correspondin

Table 1 (cont)

	Autofluorescence		Incubation with FITC insulin		Preincubation with unlabelled insulin		Diabetic sera – indirect technique	
	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
Choroid								
Stroma	0	0	0	1	0	0	0	(1)
Vessels								
Endothelial lining and basement membrane	0	0	0	4	0	1	0	3
Vessel walls	0	0	0	4	0	1	0	3
Sclera								
Stroma	0	0	1	2	(1)	1	(1)	1
Optic disc and nerve								
Vessels								
Endothelial lining and basement membrane	0	0	0	4	0	1	0	4
Vessel walls	0	0	0	4	0	1	0	4

New formed vessels and proliferative connective tissue

Basement membranes of retinal epithelia stroma and unpigmented epithelium of the ciliary processes

Basement membranes of the pigment epithelium of the iris

The inner limiting membrane of the retina

Bruch s membrane

Various structures especially the ciliary processes and the choroid were found to contain intensely fluorescing lymphocytes indicating the presence of antibodies to insulin

The loose connective tissue of the iris in diabetics showed a seemingly more pronounced perivascular cellular infiltration – mainly consisting of non fluorescent mast cells

In hyalinized vessels showing FITC insulin staining it is not always possible to distinguish between the fluorescence caused by binding of FITC labelled insulin and fluorochrome (FITC) interaction with strongly eosinophil substances in the vessel wall

Buffer incubation at different values of pH however allowed this distinction

Elastic fibers gave a non specific binding reaction in non diabetic as well as diabetic structures rich in disulphide (SS) and sulphydryl (SH) groups (Forgacs 1965)

There was a tendency to obtain a weaker degree of fluorescence with FITC labelled diabetic IgG sera fraction – using nearly the same ratio of fluorochrome protein – than with fluorescein conjugated insulin The localization of the former showed slightly different areas of fluorescence than the latter Hyalinized vessel walls in particular had a tendency to nodular distribution of fluorescence with diabetic gammaglobulin which was not seen with FITC insulin

All structures rich in matter containing carbohydrate for example glycoprotein were weakly fluorescent both in diabetic and non diabetic eyes

It was possible to demonstrate antibodies to insulin in the tissue and to block these binding reactions of the tissue by previous incubation with non conjugated insulin (see illustrations) As a consequence the difference in the intensity of fluorescence observed might be regarded as a measure of insulin – insulin antibody interaction

These results have been confirmed in autoradiographic studies on the same material

Our findings with the immunofluorescent techniques employed have shown insulin insulin antibody reaction which might be a contributory factor in the development of the pathological lesions in the diabetic eye

to autofluorescence) by the application of higher levels (1,000 fold of the above mentioned insulin concentration) of unlabelled insulin in preincubation assays As expected the most obvious attenuation of fluorescence took place in diabetic tissue

Indirect staining with gammaglobulin (IgG) fraction from diabetic sera

Using indirect staining methods with FITC conjugated diabetic gamma globulin fractions isolated from pool or single diabetic sera (compared with fractions of normal sera labelled with FITC) the following results were obtained

In diabetic eyes practically the same localization was found as that with FITC insulin but of varying intensity (see Table I)

For control in diabetic eyes using the indirect technique with non diabetic FITC-labelled sera there was no fluorescence

Non diabetic eyes presented no or only slight binding of gamma globulin from diabetic sera (see Table 1)

Discussion

It has been shown previously that insulin given regularly during a certain period of time will induce the formation of insulin antibodies *(Deckert* 1964)

By the use of immunofluorescent techniques insulin binding reactions have also been demonstrated in patients who have never received exogenous insulin *(Blumenthal et al* 1964)

Binding of insulin and of gammaglobulin from diabetic sera has been observed in muscle tissue from diabetic patients never treated with insulin *(Werner* 1968b)

In blood smears from non diabetic schizophrenic patients receiving insulin shock therapy over a long period of time it has been possible by FITC insulin reactions to observe the development of insulin antibodies during the course of treatment localized to lymphocytes *(Werner* 1968c)

In the present material all diabetic patients have received exogenous insulin It is therefore impossible on the basis of this material to discuss the possible involvement of autoimmune phenomena

As mentioned autofluorescence did not interfere with any of the fluorescent reactions

Applying FITC labelled insulin to histological sections of diabetic eyes the following structures gave rise to the most pronounced fluorescence

The endothelial lining the basement membrane and the walls of the vessels in the ciliary body iris retina choroid as well as retrobulbar fat

and non diabetic eyes II Autoradiography using I^{125} – labelled insulin and application of histochemical procedures Acta ophthal 47 956 971

Werner A U (1968)a Immunohistological methods using FITC-labelling of insulin, and IgA IgG and IgM fractions of diabetic sera In press

Werner A U (1968)b Personal observation

Werner A U (1968)c Paper in preparation

Summary

Immunohistological methods implying the use of FITC conjugated insulin and diabetic IgG fraction labelled with FITC and applied to 14 non diabetic and 30 diabetic eyes showed characteristic patterns of fluorescence due to insulin insulin antibody interaction in the diabetic specimens investigated

The intensity of fluorescence was most pronounced in the endothelial lining the basement membranes and the walls of the vessels in the ciliary body iris retina and choroid as well as in retrobulbar fat

Bright fluorescence was also seen in new formed vessels and proliferative connective tissue in basement membranes of the retinal epithelia stroma and unpigmented epithelium of the ciliary processes in basement membranes of pigment epithelium of the iris in the inner limiting membrane and in Bruch s membrane

These insulin insulin antibody reactions bear a resemblance to other immunological reactions causing vascular disease and connective tissue lesions and might be a contributory factor in the development of the pathological lesions occurring in the diabetic eye

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Larsen H W & A U Werner (1969) Immunohistological studies on human diabetic

The specimens investigated were obtained at autop y or after enucleation and the eyes formalin fixed and paraffin embedded

The following methods were employed

Autoradiograms of eye sections were prepared according to the method of *Werner* (1968) The PAS stained sections were incubated with I¹²⁵ labelled pure pig insulin in a concentration of 150 micro units/ml incubating medium (1 micro unit = 0 04 × 10⁻⁴ mg insulin incubating medium = 0 01 molar pho phate buffer pH 7 1) the final radioactivity amounting to 0 25 microCi/ml Time of incubation was 30 minutes Nuclear K emulsion (Ilford) was used for coating the sections Time of exposure was about 10 days at + 4° C The auto radiograms were developed with Amidol (diaminophenol hydro hloride) The nuclei were stained with haemalum

Various histochemical procedures were employed PAS staining with and without pectinase and diastase digestion silver impregnation of reticulin fibers *orcein staining* of elastic fibers demonstration of acid mucopolysaccharides by alcian blue staining acridine orange fluorescence for determination of nucleic acids

The *strength* of the insulin solution used for preincubation assays was 150 microCi/ml phosphate buffer within the limits of postprandial values of plasma insulin in normals A solution 1 000 times this strength was also employed

Results

The results are shown in Figs 1 14 and listed in Table 1 The degree of insulin binding is indicated by the silver grain density and this is graded arbitrarily from 0 to 4

Autoradiography (ARG)

Ciliary body

In diabetic eyes diffuse distribution of blackening (grade 1) was produced over the unpigmented ciliary epithelium and basement membrane (grade 2) The stroma showed no binding Marked accumulation of silver grains occurred in the inner part of the vessel walls corresponding to endothelial lining and base ment membrane (grade 3) The remaining part of the vessel wall showed grade

Similar findings were not encountered in non diabet c eyes

Iris

Diabetic eyes There was distinct binding (grade 3) to the basement membrane

From the Steno Memorial Hospital (Niels Steensens hospital)
Gentofte Denmark (Chief Jac E Poulsen)
and the Ophthalmic Pathology Laboratory Rigshospitalet
Copenhagen Denmark (Chief S Ry Andersen)

IMMUNOHISTOLOGICAL STUDIES ON HUMAN DIABETIC AND NON-DIABETIC EYES

II Autoradiography using I^{125} labelled insulin and application of histochemical procedures

BY

H W LARSEN and A U WERNER

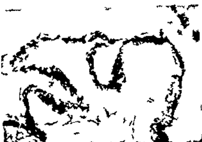
In a previous paper investigations with fluorescein isothiocyanate (FITC) - conjugated insulin were carried out on human diabetic and non diabetic eyes in order to evaluate insulin and insulin antibody binding reactions

To obtain supplementary information concerning insulin binding in eye tissue autoradiograms (ARG) using I^{125} labelled insulin were made simultaneously with periodic acid Schiff (PAS) staining on serial sections of the same material as used in the previous study

Material and Methods

The series consisted of 14 non diabetic eyes and 30 diabetic eyes with retinopathy The non diabetic group consisted of 8 men and 6 women the diabetic group of 16 men and 14 women The mean age was 50 (1 84) in non diabetics and 53 in diabetics (25 85) Duration of diabetes was from 7 to 55 years mean 22 years 8 of the patients were diabetic for 25 years or more

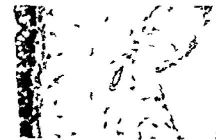
Received December 17th 1968















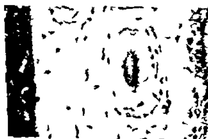


Fig 1 The ciliary processes from an aged non diabetic person
There is a slight degree of PAS positivity
PAS + HA (× 60) Lab No 6 67

Fig 2 Ciliary processes from a diabetic aged 39 years illustrating pronounced PAS positive reaction of the basement membranes
PAS + HA (× 60) Lab No 476 62

Fig 3 Ciliary process in high power view from a non diabetic person showing the effect of simultaneous PAS staining and autoradiographic exposure of the section to iodine 125 labelled insulin
Minimal background minimal silver grain scattering and no binding to vessels or basement membranes
ARG PAS + HA (× 600) Lab No 6 67

Fig 4 Ciliary process with vessels in close view from a diabetic The preparation was handled in the same way as that of fig 3
An accumulation of silver grains corresponds to the endothelial lining
ARG PAS + HA (× 600) Lab No 681/66

Fig 5 Leucofuchsin staining of part of the iris from a normal person showing practically no colouring of the basement membrane of the iris or the vessels
PAS + HA (× 390) Lab No 6 67

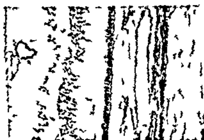
Fig 6 The iris from a diabetic stained by PAS An intense colouring with leucofuchsin demonstrated glycoprotein containing material in the basement membranes of the iris and in the vessels
PAS + HA (× 390) Lab No 476 62

Fig 7 Section of the iris from a non diabetic person
Autoradiogram using iodine 125 labelled insulin combined with PAS staining Minimal amounts of silver grains are evenly distributed throughout the section and background
No binding of insulin observed
ARG PAS + HA (× 450) Lab No 6 67

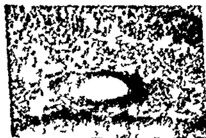
Fig 8 Autoradiographic exposure of a diabetic iris using insulin I^{125}
The preparation presents condensation of silver grains over the basement membrane of the iris and over the vessels
ARG PAS + HA (× 450) Lab No 681/66

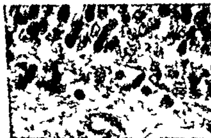












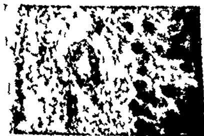




Fig 9 Detail showing vessel from the iris in a diabetic eye
The section was treated in the same way as in fig 8
There is heavy deposition of silver grains corresponding to the endothelial lining and basement membrane of the vessel
Grain density could be noted in the vessel wall
ARG PAS + HA (× 600) Lab No 267/62

Fig 10 PAS staining of the retina choroid and sclera from an aged non diabetic person Minimal PAS reactivity of the vessel walls and the inner limiting membrane
PAS + HA (× 300) Lab No 6/67

Fig 11 Autoradiographic image of the retina choroid and sclera from a non diabetic person
Incubation of the section with nuclide (I^{125}) marked insulin
No deposits of grains could be seen
ARG PAS + HA (× 300) Lab No 6/67

Fig 12 The retina from a diabetic displaying a marked PAS positivity of a retinal artery The inner limiting membrane is also PAS reactive
PAS + HA (× 450) Lab No 335/60

Fig 13 Close view of a detached retina from a diabetic Autoradiographic exposure to I^{125} labelled insulin combined with PAS staining
Heavy silver grain density over the vessel especially along the endothelial lining the internal limiting membrane of the retina and the site of retinal detachment
ARG PAS + HA (× 600) Lab No 267/62

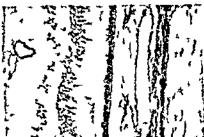
Fig 14 High power view of a small vessel in the retina of a non diabetic person No binding of I^{125} tagged insulin occurred
ARG PAS + HA (× 1500) Lab No 6/67

Fig 15 Retinal vessel of approximately the same caliber as that shown in fig 14 but from a diabetic
Pronounced binding of labelled insulin to the endothelial lining and basement membrane is demonstrated
ARG PAS + HA Magnification × 1500 Lab No 681/66

Fig 16 Binding of marked insulin to a minor retinal *vessel in a diabetic eye* Silver grain density noted over endothelial lining and basement membrane
ARG PAS + HA (× 750) Lab No 596/66

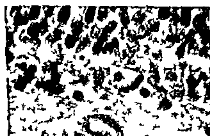

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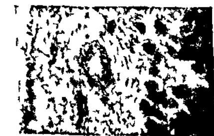

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The section was treated in the same way as in fig 8
There is heavy deposition of silver grains corresponding to the endothelial lining and basement membrane of the vessel
Grain density could be noted in the vessel wall
ARG PAS + HA (× 600) Lab No 267/62

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PAS + HA (× 300) Lab No 6/67

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Fig 12 The retina from a diabetic displaying a marked PAS positivity of a retinal artery The inner limiting membrane is also PAS reactive
PAS + HA (× 450) Lab No 335/60

Fig 13 Close view of a detached retina from a diabetic Autoradiographic exposure to I^{125} labelled insulin combined with PAS staining
Heavy silver grain density over the vessel especially along the endothelial lining the internal limiting membrane of the retina and the site of retinal detachment
ARG PAS + HA (× 600) Lab No 267/62

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ARG PAS + HA (× 1500) Lab No 6/67

Fig 15 Retinal vessel of approximately the same caliber as that shown in fig 14 but from a diabetic
Pronounced binding of labelled insulin to the endothelial lining and basement membrane *is demonstrated*
ARG PAS + HA Magnification × 1500 Lab No 681/66

Fig 16 Binding of marked insulin to a minor retinal vessel in a diabetic eye Silver grain density noted over endothelial lining and basement membrane
ARG PAS + HA (× 750) Lab No 596/66

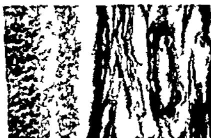

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Fig 17 Serial section of the same structure as in fig 16 showing the inhibition of binding effects obtained by prior incubation with unlabelled insulin
ARG PAS + HA (× 750) Lab No 596/66

Fig 18 Proliferative diabetic retinopathy Pronounced insulin I^{125} binding to the neo vascularizations
ARG PAS + HA Magnification × 1500 Lab No 681/66

Fig 19 Proliferative lesions in a diabetic eye In this section heavy density of silver grains corresponding to the vessels and some deposition on the connective tissue elements could be visualized
Iodine 125 labelled insulin incubation followed by autoradiography
ARG PAS + HA (× 1275) Lab No 267/62

Fig 20 PAS staining of the choroid from a 70 year old non diabetic person
There is some colouring of Bruch s membrane The choroidal vessels are moderately hyalinized
PAS + HA Magnification × 450 Lab No 6/67

Fig 21 PAS staining of the choroid from a diabetic demonstrating massive PAS positivity of the vessels and Bruch s membrane
Nearly complete hyalinization of some of the small vessels
PAS + HA (× 750) Lab No 267/62

Fig 22 The choroid from a diabetic showing simultaneously applied PAS staining and autoradiographic exposure of the section to labelled insulin
Silver grain deposits corresponding to the endothelial lining basement membranes and vessel walls
ARG PAS + HA Magnification × 600 Lab No 596/66

Fig 23 Detail of section from the same choroid as in fig 22
Pronounced PAS positivity of the hyalinized vessels and silver grain density in these areas I^{125} marked insulin incubation
ARG PAS + HA (× 900) Lab No 596/66

Fig 24 View of minor choroidal vessels in a diabetic Incubation with insulin I^{125} This section shows silver grain accumulation corresponding to the endothelial linings and basement membranes together with extreme PAS positivity of vascular structures
ARG PAS + HA (× 1500) Lab No 267/62

vessels walls as found in the retina There was grade 2 binding of insulin to fat cell membranes

No blackening occurred in non diabetic eyes

Preincubation with unlabelled insulin

Sections preincubated with unlabelled insulin showed no binding when exposed to labelled insulin

Histochemical procedures

PAS staining

Staining with PAS revealed more intensely coloured vessels and basement membranes in diabetic than in non diabetic eyes (See Table 1)

Other histochemical methods

With orcein staining the elastic fibers in diabetics appeared shorter and coarser than in non diabetics

Examination with alcian blue staining acridine orange fluorescence and silver impregnation to demonstrate respectively acid mucopolysaccharides nucleic acids and reticulin fibers permitted no definite conclusions with respect to differences between diabetic and non diabetic material

Discussion

Autoradiograms (ARG) made with I^{125} labelled insulin on diabetic eye sections showed an accumulation of silver grains to practically the same structures as were found to bind fluorescein isothiocyanate (FITC) labelled insulin Both procedures mentioned demonstrate the interaction between insulin and insulin antibodies in tissue The preincubation assays with unlabelled insulin confirm this conclusion in both studies

The most pronounced density of silver grains in the autoradiograms was located to the following structures

The endothelial lining basement membranes and wall of the vessels in the ciliary body iris retina and choroid as well as retrobulbar fat.

Neovascularizations and proliferative connective tissue

Basement membranes of retinal epithelia and of unpigmented epithelium of the ciliary processes.

Basement membrane of the pigment epithelium of the iris

The inner limiting membrane of the retina

of the pigment epithelium and/or the dilator muscle of the iris No significant binding was observed to the loose connective tissue grade (1) There was pronounced accumulation over the endothelial lining and basement membrane of the vessels (grade 3) while the rest of the vessel wall was grade 2 There was slight perivascular binding

In cases where the pigment epithelium was vacuolated and presented a lacy appearance a moderate degree of insulin binding was found to the degenerated cells (grade 1)

No silver grain fogging was visible in non diabetic eyes

Cornea and Lens

Diabetic as well as non diabetic eyes showed no significant degree of blackening

Retina

In diabetic eyes accumulation of silver grains was observed over the inner limiting membrane (grade 1 2) and the other layers of the retina (grade 1) Very heavy fogging was noticed over the vessels (grade 3) especially over the endothelial and basement membrane structures (grade 4)

In non diabetic eyes similar findings were not encountered

Proliferative diabetic lesions

Marked deposits of silver grains were seen over new formed vessels (grade 4) and proliferative connective tissue (grade 1 3)

Bruch s membrane

In diabetic eyes a moderate binding (grade 2) was present but there were no deposits in non diabetic eyes

Choroid

In diabetic eyes the film showed accumulation of silver grains in vessel endothelial lining and basement membrane (grade 4) outer parts of the vessel walls (grade 3) and connective tissue elements (grade 1)

No blackening occurred in non diabetic eyes

Sclera

There was grade 2 accumulation in diabetic eyes grade (1) in non diabetic eyes

Optic nerve and retrobulbar fat tissue

In those sections of diabetic eyes presenting the optic disc and nerve and those containing retrobulbar fat silver grains showed the same density over the

Lens						
Capsule	1	1	0	0	0	0
Stroma	0		0	0	0	0
Retina						
Inner limiting membrane	1	?	0	1–?	0	0
Nerve fiber layer	0	1	0	1	0	0
Ganglion cell layer	0	1	0	1	0	0
Inner plexiform layer	0	1	0	1	0	0
Inner nuclear layer	0	0	0	1	0	0
Outer plexiform layer	0	1	0	1	0	0
Outer nuclear layer	0	0	0	1	0	0
Outer limiting membrane	0	1	0	1	0	0
Layer of rods and cones	(1)	2	0	1	0	0
Pigment epithelium	0	0	0	0	0	0
Vessels						
Endothelial lining and basement membrane	1	4	0	4	0	(1)
Vessel walls	(1)	4	0	3	0	(1)
Proliferative diabetic lesions						
New formed vessels						
Endothelial lining and basement membrane	–	4	–	4	–	0
Vessel walls	–	4	–	4	–	0
Connective tissue proliferation	–	3	–	2	–	0
Bruch's membrane	?	4	0	?	0	0

Table 1

	Periodic acid Schiff (PAS)		Autoradiography (ARG)		Preincubation with unlabelled insulin	
	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
Cornea						
Epithelium	0	0	0	0	0	0
Bowman s membrane	1	1	0	0	0	0
Stroma	0	(1)	0	0	0	0
Descemet s membrane	1	1	0	0	0	0
Endothelium	0	0	0	0	0	0
Ciliary body						
Neuroepithelium	0	2	0	1	0	0
Pigment epithelium	0	0	0	0	0	0
Basement membrane	(1)	4	0	2	0	0
Stroma	0	2	0	0	0	0
Vessels						
Endothelial lining and basement membrane	0	4	0	3	0	0
Vessel walls	0	3	0	2	0	0
Iris						
Stroma	0	0	0	(1)	0	0
Basement membrane	0	4	0	3	0	0
Pigment epithelium	0	0	0	0	0	0
Vessels						
Endothelial lining and basement membrane	(1)	3	0	[illegible]	0	1
Vessel walls	(1)	3	0	2	0	(1)

Lens	1	[illegible]	0	0	0	0
Capsule	0	1	0	0	0	0
Stroma						
Retina	1	[illegible]	0	1–2	0	0
Inner limiting membrane	0	1	0	1	0	0
Nerve fiber layer	0	1	0	1	0	0
Ganglion cell layer	0	1	0	1	0	0
Inner plexiform layer	0	0	0	1	0	0
Inner nuclear layer	0	1	0	1	0	0
Outer plexiform layer	0	0	0	1	0	0
Outer nuclear layer	0	1	0	1	0	0
Outer limiting membrane	0	1	0	1	0	0
Layer of rods and cones	(1)	[illegible]	0	0	0	0
Pigment epithelium	0	0	0	0	0	0
Vessels						
Endothelial lining and basement membrane	1	4	0	4	0	(1)
Vessel walls	(1)	4	0	3	0	(1)
Proliferative diabetic lesions						
New formed vessels						
Endothelial lining and basement membrane	–	4	–	4	–	0
Vessel walls	–	4	–	4	–	0
Connective tissue proliferation	–	3	–	2	–	0
Bruch's membrane	[illegible]	4	0	[illegible]	0	0

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Stroma	0	(1)	0	0	0	0
Descemet s membrane	1	1	0	0	0	0
Endothelium	0	0	0	0	0	0
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Neuroepithelium	0	2	0	1	0	0
Pigment epithelium	0	0	0	0	0	0
Basement membrane	(1)	4	0	2	0	0
Stroma	0	2	0	0	0	0
Vessels						
Endothelial lining and basement membrane	0	4	0	3	0	0
Vessel walls	0	3	0	2	0	0
Iris						
Stroma	0	0	0	(1)	0	0
Basement membrane	0	4	0	3	0	0
Pigment epithelium	0	0	0	0	0	0
Vessels						
Endothelial lining and basement membrane	(1)	3	0	3	0	1
Vessel walls	(1)	3	0	2	0	(1)

Bruch s membrane

Silver grain distribution over areas with infiltrative cells – mostly lymphocytes – was seen in many structures of the diabetic eye

Elastic fibers showed an insulin binding capacity in non diabetic as well as in diabetic structures which are rich in disulphide(SS) and sulphydryl(SH) groups This is in accordance with findings reported by *Buse et al* (1965)

Polysaccharides neutral mucopolysaccharides muco and glycoproteins glycolipids unsaturated lipids and phospholipids are classified as tissue components giving a PAS positive reaction

PAS positive lesions are characteristic of diabetic angiopathy The vessels of all diabetic eye structures show damage of varying degree including focal alterations of the vessel wall endothelial proliferation splitting or homogenous thickening of the basement membranes fibrinoid degeneration and hyalinization and occasionally even calcification However none of these pathological changes individually or collectively are specific for diabetes *(Ashton* 1963)

The presence of perivascular infiltration of lymphocytes eosinophil granulocytes and histiocytes in ciliary processes choroid retina and proliferative lesions suggests that an immune mechanism is involved

Antibodies to insulin have been found in the IgA IgG and IgM fractions of diabetic sera The haemagglutinating and complement fixing insulin antibodies are found in the IgG fraction of anti insulin sera whereas the anaphylactic antibodies belong to the IgA type of immunoglobulin *(Corcos et al* 1965) IgM insulin binding antibodies have been detected in sera of diabetic patients with acute local reactions to insulin shortly after the insulin therapy was initiated *(Devlin et al* 1965 1966) The response to antigenic stimuli is in the last analysis determined by genetic influences *(Day* 1966 *Cinader et al* 1967 *Kniker* 1967 a and b)

Antigen antibody complexes have not with certainty been proved to induce pathological lesions but might be a contributory factor to vessel injury in the diabetic organism

Another perhaps essential cause could be the induction of antibodies against the altered glyco or lipoprotein components of the diabetic vessels or basement membranes

The strong periodic acid Schiff reativity seen in basement membranes in diabetics is supposed to be caused by the polymerization of almost insoluble complexes of polysaccharide protein

Disturbance of the normal balance between depolymerization and repolymerization equilibrium in the ground substance (free matrix of intercellular material) will give rise to shifts in the ion exchange – sodium and in particular potassium – and the cellular water metabolism of the tissue

A depolymerization of ground substance is practically always accompanied by an increase in vessel wall permeability

Table 1 (cont)

	Periodic acid Schiff (PAS)		Autoradiography (ARG)		Preincubation with unlabelled insulin	
	Non diabetic	Diabetic	Non diabetic	Diabetic	Non diabetic	Diabetic
Choroid						
Stroma	0	(1)	0	(1)	0	0
Vessels						
Endothelial lining and basement membrane	1	4	0	4	0	1
Vessel walls	(1)	3	0	3	0	0
Sclera						
Stroma	1	2	(1)	2	0	0
Optic disc and nerve						
Vessels						
Endothelial lining and basement membrane	1	4	0	4	0	0
Vessel walls	(1)	4	0	3	0	0

Buse M G D J Jones & W C Worthington (1965) Uptake of insulin labelled with iodine 131 by elastic tissue in vitro Nature 205 1176 1178
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Devlin J G & D K O Donovan (1966) Preferential beef/pork insulin binding capacity Radioimmunoelectrophoretic and chromatographic data in patients with dermal reactions to insulin Diabetes 15 790 797
Kniker W (196[illegible])a Insulin and its immunologic reactions In *Kimura S J & W M Caygill* Vascular complications of diabetes mellitus with special emphasis on microangiopathy of the eye The C V Mosby Company Saint Louis p 184 189
Kniker W (19[illegible])b Immunogenic vasculitis is it a part of diabetes mellitus? In *Kimura S J & W M Caygill* Vascular complications of diabetes mellitus with special emphasis on microangiopathy of the eye The C V Mosby Company Saint Louis p [illegible]01 209
Werner A U (1968) Autoradiographic immunohistological methods using I^{125} labelled insulin In press
Werner A U & H W Larsen (1969) Immunohistological studies on human diabetic and non diabetic eyes I Fluorescent labelling of insulin and insulin antibodies Acta ophthal 47 934 935

Permeability disturbances could be one of the causal factors in diabetic retinopathy (*Ashton* 1967) A tendency *of the* vessel *walls to oedema might* produce anoxia in adjacent tissue thereby further favouring glycolytic metabolism These event may start a vicious circle in the already altered metabolic pathways of the diabetic organism inducing or exaggerating vascular damage.

Interaction of these primary elements and other yet unknown contributory mechanisms could play a role in the pathogenesis of the generalized diabetic angiopathy

Summary

Immunohistological *methods implying the use of autoradiography* with I^{125} labelled insulin and various histochemical procedures applied to 14 non diabetic and 30 diabetic eyes showed characteristic silver grain accumulation due to insulin – insulin antibody interaction in the diabetic specimens investigated

The silver grain accumulation was most pronounced in the endothelial lining basement membranes and walls of the vessels in the ciliary body iris retina and choroid as well as in the retrobulbar fat

Deposits of silver grains were also seen in new formed vessels and proliferative connective tissue basement membranes of retinal epithelia and of unpigmented epithelium of the ciliary processes basement membrane of *the* pigment epithelium of the iris the inner limiting membrane of the retina and Bruch s membrane

A strong PAS positivity was found in basement membranes and vessel walls *in the diabetic specimens investigated*

No definite differences between diabetic and non diabetic eyes were found on using various other histochemical methods

The pathogenesis of vascular damage in the diabetic eye is discussed on the basis of the findings

References

Ashton N (1963) Studies of the retinal capillaries in relation to diabetic and other retinopathies Brit J Ophthal *47 521 538*

Ashton N (1967) Oxygen and the growth and development of retinal vessels In vivo and in vitro studies In *Kimura S J & W M Caygill* Vascular complications of diabetes mellitus with special emphasis on microangiopathy of the eye *The* C V Mosby Company Saint Louis p 3 32

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vitreous humors in patients suffering from malignant melanoma of the choroid was suggested by *Bala s* (1964) who found indications of such a correlation in a human eye which was enucleated on account of the presence of a malignant tumor

The present study was undertaken in order to investigate if an elevated level of sialic acid in the aqueous humor and the vitreous is a constant finding in malignant tumor of the choroid and if so whether a relatively simple diagnostic test might be worked out on this basis

Material

Normal eyes This group may be divided into two different categories The first one consisted of samples of aqueous humor taken from an autopsy material The samples were aspirated 10 46 hrs after death using the technique described later The various causes of death are listed in table I

The second category comprised samples of aqueous humor and vitreous from people who died suddenly and who had been brought to the Institute of Forensic Medicine in Copenhagen

The samples were all taken within 1 hour after death The data of these patients are given in table II

Pathological eyes Two different groups of pathological eyes were examined The first group consisted of eyes in which a malignant tumor had been diagnosed the second one of eyes with nonmalignant eye disorders The technique of aspiration is described below

Aspiration technique

The same technique was used on enucleated eyes and on eyes *in situ*

I Aqueous humor The anterior chamber was punctured at the limbus corneae with a 23 g needle mounted on a graduated micropipette (Haska Bern) Owing to the capillarity the pipette fills automatically The aspirated volume is read directly

II Vitreous The aspiration was carried out with a 21 g needle mounted on a disposable 2 ml syringe The puncture was performed approximately 5 mm from the limbus corneae anteriorly to the insertion of the lateral rectus muscle When the point of the needle was seen in the middle of the vitreous 0 4 0 8 ml of central vitreous was carefully sucked out

Immediately after aspiration all samples were frozen at -20° C Until the analyses were performed the samples were kept at this temperature

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University of Copenhagen Denmark
(Head S Ry Andersen)

SIALIC ACID IN THE AQUEOUS HUMOR AND THE VITREOUS OF NORMAL HUMAN EYES AND OF EYES WITH MALIGNANT MELANOMA OF THE CHOROID

BY

IENS FALBE HANSEN and JUDITH KAROSSA DEGN

Sialic acid is one of the constituents of protein bound carbohydrate in serum (*Werner & Odin* 1952 *Odin* 1955 *Martensson Raal & Svennerholm* 1958)

Since the same protein spectrum is encountered in the aqueous humor as in blood serum although the protein concentration of the former is much lower the presence of sialic acid might be expected in the aqueous humor This has indeed turned out to be the case in various animal species as demonstrated by *Bala s et al* (1959) *Takki-Luukkainen & Miettinen* (1959) *Bala s & Sundblad* (1960) and *Schmidt* (1960)

Similar glycoproteins are found in the vitreous of many animals (*Bala s et al* 1959 *Bala-s & Sundblad* 1960 *Schmidt* 1961)

The concentration of glycoproteins in serum has been shown to increase under various pathological conditions (*Seibert et al* 1947 *Winzler et al* 1948 *Winzler & Smyth* 1948) notably in malignant diseases and in pyogenic infections It was a near thought that similar changes in the glycoproteins of the aqueous humor might occur in various eye disorders

A possible elevation of the concentration of sialic acid in the aqueous and

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Immediately after aspiration all samples were frozen at − 20° C. Until the analyses were performed the samples were kept at this temperature

Methods

Centrifugation

The aqueous samples were centrifuged for 1 hour at 4° C in a refrigerated MSE centrifuge at 45 000 × g

The vitreous samples were centrifuged at 4° C in a Beckmann Spinco L 50 preparatory ultracentrifuge for 2 hours at 105 000 × g

Dialysis

All samples aqueous as well as vitreous were dialysed in a microdialysis apparatus (Kunz Copenhagen) at 37° C for approximately 2 hrs against 4 l of destilled water

This step is extremely important as it has been shown by *Falbe Hansen* & *Balazs* (1963) that ascorbic acid after acid hydrolysis interferes to a large extent with thiobarbituric acid in the assay of sialic acid

Determination of sialic acid

After hydrolysis for 1 hour at 80° C with 0 1 N HCl the sialic acid content was determined by the thiobarbituric acid method of *Aminoff* (1961)

Determination of sialic acid

Protein determination was carried out according to the method of *Lowry et al* (1951)

Both analytical methods had to be adapted to much smaller sample volumes than usual With the use of Lang Levy micropipettes this presented no problems the accuracies being equal to those of the macromethods for sample volumes down to 20 μl The spectrophotometric readings were performed with a Zeiss PMQ II spectrophotometer using semimicro quartz cells

All analyses were carried out as duplicate determinations

Results

Autopsy material (Table I)

Aqueous humor was aspirated during routine autopsy The results of the analyses are given in table I The values of both protein and sialic acid show many large variations from the mean Besides the values are higher than those found by other investigators in ocular fluids from various species (*Amsler et al* 1955 *Balazs et al* 1959 *Balazs* & *Sundblad* 1959)

Table I
Aqueous humor taken from autopsy material

case		age (years)	cause of death	sialic acid μg per ml	protein mg per ml	interval between death and taking of sample (hours)
♂	1	76	polyarthritis	30.0	2.27	1?
♂	2	0	cardiac fail	40.2	2.36	28
♂	3	57	cardiac fail	39.5	1.95	28
♀	4	0	cardiac fail	33.8	1.17	30
♂	5	90	cardiac fail	145.0	2.63	28
♀	6	57	cancer pulm	44.0	1.36	28
♀	7	64	diabetes	83.4	2.21	22
♀	8	72	thromb cerebri	127.0	2.46	33
♂	9	64	cancer vesicae	72.6	1.57	19
♂	10	47	thromb a pulm	50.9	1.36	28
♀	11	49	cancer pancr	77.5	1.63	20
♀	12	48	tub pulm	141.0	6.80	18
♂	13	72	cardiac fail	77.5	4.55	21
♀	14	52	cardiac fail	62.8	2.92	15
♂	15	65	diabetes	63.5	2.38	29
♂	16	73	cardiac fail	131.0	2.28	24
♂	17	53	?	71.0	1.45	10
♂	18	52	?	48.8	1.32	46
♀	19	84	cardiac fail	49.2	0.96	18
♂	20	37	cancer pulm	46.8	1.13	31
			mean	74.3 ± 34.8	2.20 ± 1.38	

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In accordance with the above speculations the material taken within 1 hour after death (Table II) shows considerably lower values both for protein and sialic acid than does the autopsy material As already mentioned the figures of the aqueous humor are however slightly higher than usually stated This may be due to diffusion *post mortem* This may also account for the unusually wide distribution of the individual results which has no statistical explanation in the accuracies of the analytical methods used In this connexion it is interesting that aqueous samples taken from comparatively normal *living* humans viz cataract patients (Table III) have a lower protein mean value (0 39 mg per ml) than the aqueous samples of table II

Another possibility which cannot be ruled out is that the mode of death or merely death in itself may alter the protein concentration of the aqueous humor Thus it is wellknown that for instance death by strangulation causes multiple haemorrhages in various eye tissues It is obvious that this may lead to leaking of blood constituents into the aqueous This may explain the very high protein concentration in the aqueous of case 1163 (Table II)

In the nonmalignant eye disorders (Table III) the difference between the cases of haemorrhagic glaucoma and the other cases is striking Highly elevated values of both sialic acid and protein are constant findings Although there is no blood to be seen in the aqueous or vitreous it seems very probable that there has been a leaking of blood constituents for a long period from the many dilated and newly formed blood vessels Again it is remarkable that there is no direct relationship between the concentrations of sialic acid and protein In fact the highest protein figure measured is from a vitreous sample (case 17 Table III) in which the concentration of sialic acid is not increased

One of the purposes of this study has been to establish whether an increased concentration of sialic acid in the aqueous humor is a constant finding in eyes with malignant melanoma of the choroid This turned out not to be the case (Table IV) Elevated values are found in only three out of twelve cases In contrast the figures of both sialic acid and protein are constantly higher than normally in the vitreous of the examined melanoma eyes In one case (P P *Table IV) the* concentration is increased a hundred times As in the cases of nonmalignant eye disorders (Table III) the values of protein and sialic acid vary independently of each other In the aqueous of two eyes with metastases from malignant tumors elsewhere in the body nothing abnormal was *found*

The three cases of malignant melanoma in which elevated values of sialic acid in the aqueous were found belong to two different cell types and they also differ as to the site of the tumor Two of them (P I *and* H J Table IV) have however one characteristic in common they are the largest tumors in the material and they are considerably larger than any of the other tumors It is interesting that these two tumors also have *the highest* concentration of sialic acid in the vitreous This seems to indicate that size and not cell type or location is

Fresh material taken within 1 hour after death (Table II)

As the above material was considered unsatisfactory probably because of the long interval between death and the taking of the samples it was decided to get fresher material This was possible through the aid of the Institute of Forensic Medicine in Copenhagen Here samples from patients who had died suddenly were taken within 1 hour after death The results of the analyses are given in table II Although the distributions are still wide the mean values are much lower than in the autopsy material

Material from eyes with nonmalignant eye disorders (Table III)

A number of analyses have been performed on aqueous humor from cataract eyes Only in one case was an elevated value of sialic acid found The protein figures were lower than those of the normal material

In the cases of haemorrhagic glaucoma nearly all values of sialic acid and protein both in the aqueous and in the vitreous were abnormally high

In the cases of buphthalmia choroidal detachment and choroidal haemorrhage normal concentrations were found

Material from eyes with malignant tumors (Table IV)

Twelve eyes with malignant melanoma of the choroid were examined and two eyes with ocular metastases In the melanoma eyes increased concentrations of sialic acid and protein in the vitreous was a fairly constant finding In the aqueous it occurred in only three cases

No abnormal values were found in the eyes with metastases

Discussion

The high values of sialic acid and protein found in the aqueous humor of the autopsy material (Table I) is probably due to a diffusion of macromolecules into the aqueous from blood and vitreous *post mortem* Although no direct relationship could be found between the concentrations and the length of the interval between death and the taking of the samples it seems reasonable to assume that the risk of contamination by diffusion is smaller the sooner after death the samples are taken

In many instances the values of sialic acid and protein are more or less equally enhanced but in other cases they seem to vary independently of each other This may be attributed to an uneven diffusion of protein molecules of varying size

♀	1f	77	cardiac fail	24 9	1 03	30 3	2 90
♀	649	59	cardiac fail	13 4	0 86	15 5	0 07
♀	630	67	hæmorrh cerebri	6 0	0 9	3 7	0 26
♀	671	65	cardiac fail	18 3	0 67	28 0	0 33
♂	6 ?	68	cardiac fail	33 3	0 91	61 3	2 84
♀	507	69	cardiac fail	26 7	0 72	18 0	1 34
♂	7 C	67	cardiac fail	24 2	0 39		
♂	7 0	47	cardiac fail	18 5	0 79	23 9	2 09
♂	45	5	cardiac fail	27 6	2 70	27 4	2 00
♂	753	53	cardiac fail	29 9	2 01	26 9	1 39
♂	913	66	cardiac fail	19 2	0 53	13 2	0 53
♂	598	57	cardiac fail	49 3	0 37	34 3	0 40
♀	961	69	cardiac fail	26 3	0 71	29 4	0 39
♂	910	74	cardiac fail	71 0	0 47	57 5	1 08
♂	504	4	contus cerebri	23 2	0 22	54 7	1 25
♀	961	45	cardiac fail	19 3	0 62		
♀	531	75	cardiac fail	15 1	0 75	41 3	1 40
			mean	23 5 ± 14 7	0 95 ± 0 75	27 3 ± 14 6	1 06 ± 0 80

Table II

Aqueous humor and vitreous taken within 1 hour after death

case		age (years)	cause of death	AQUEOUS		VITREOUS	
				sialic acid µg per ml	protein mg per ml	sialic acid µg per ml	protein mg per ml
♂	1273	53	*suffocatio per* obstruct int	44 0	0 94	15 3	0 38
♂	1423	59	cardiac fail	26 6	1 18	43 0	0 56
♀	1297	60	venefic barbit	18 9	0 69	20 7	0 38
♀	1264	56	cardiac fail	18 6	0 49	25 6	0 73
♂	826	66	cardiac fail			37 2	2 01
♂	1057	66	venefic CO	9 0	0 78	7 3	0 44
♂	1058	77	cardiac fail	13 2	0 73	23 6	0 49
♂	1193	67	rupt aortae	21 8	1 19	19 2	1 19
♂	1163	18	suffocatio per compressionem	6 3	2 78	6 5	1 52
♂	1174	57	cardiac fail	9 7	0 34	13 8	0 19
♂	1164	49	?	15 4	2 79	14 8	0 39
♂	1287	45	?	25 0	0 21	36 4	
♂	05	45	cardiac fail	4 4	0 88	20 3	0 54
♀	715	64	hæmorrh cerebri	27 4	2 08	37 6	2 42
♂	725	78	?	57 2	1 31	29 5	0 35

Table IV

Aqueous hum r an l vitrecus from human eyes with malignant eye dis ases M M Mal gnant melan ma The un lerlined val es are s gnif cantly elevated The terms anterior and posterior refer to the l cation of the tumor in respect of the equator of the eye bulb

case	age (years)	type of tumor	location of tumor	AQUEOUS		VITREOUS	
				sialic acid g per ml	protein mg per ml	sialic acid g per ml	protein mg per ml
♂ K I	44	M M spindle B	anterior	19 8	1 95	*495 0*	*11 75*
♂ I I	91	M M spindle B	posterior	*560 0*	*96 90*	*9890 0*	38 20
♂ J N	0	M M spindle B	posterior	90 8	0 96		
♂ C C	60	M M mixed	posterior	3 1	0 94	*90 0*	9 60
♂ H J	68	M M mixed	anterior	*593 0*	*4 36*	*690 0*	*7 00*
♂ A I	33	M M mixed	anterior	47 2	1 50		
♀ H K	73	M M mixed	posterior	*71 9*	*4 48*	*552 0*	1 99
♀ I I	35	M M spindle B	posterior	16 0	0 74	*69 9*	*3 31*
♀ I K	98	M M mixed	anterior	49 8	1 47	*246 0*	*9 14*
♂ A H	59	M M mixed	posterior	33 4	0 33		
♀ I J	79	M M spindle B	anterior	95 1	0 68		
♀ M H	64	M M mixed	posterior	15 0	1 35	*489 0*	*9 5*
♂ J K	79	Metast ad ocul posterior (c. prostatae)	posterior	17 8	0 47		
♀ S A	41	Metast ad ocul posterior (c mammae)	posterior	32 6	0 39		

Table III

Aqueous humor and vitreous from normal human eyes In the cataract patients the aqueous was aspirated immediately before operation

The underlined values are significantly elevated

case	age (years)	eye disorder	AQUEOUS		VITREOUS	
			sialic acid µg per ml	protein mg per ml	sialic acid µg per ml	protein mg per ml
♂ C H	33	*cataract*	18.0			
♂ A A	72	cataract	27.0	0.08		
♀ M B	73	cataract	19.4	0.53		
♂ J N	58	cataract	42.4	0.76		
♀ P R	75	cataract	21.4	0.63		
♀ H P	69	cataract	*78.8*	0.39		
♂ C C	74	cataract	*42.0*	0.22		
♂ K M	64	cataract	6.1	0.19		
♀ G A	65	cataract	2.7	0.17		
♀ A H	77	cataract	8.4	0.57		
♀ A B	74	glauc hæmor	*322.0*	2.02		
♀ F J	77	*glauc hæmo-*	*248.0*	*6.95*		2.40
♀ M D	81	glauc hæmor	*88[illegible].0*	*10.10*	29.8	*19.25*
♂ H J	62	glauc hæmor	*412.0*	*5.95*	*738.0*	*14.00*
♂ C R	64	glauc hæmor	24.9	0.78	*157.[illegible]*	*5.20*
♀ T	0	buphthalmia	33.0	0.51	26.0	0.98
♂ F P	51	*choroid detach*	22.8	0.82		
♂ S I	71	choroid hæmor	26.7	0.27		

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responsible for the appearance of sialic acid containing compounds in the aqueous As an elevated concentration in the vitreous seems to be a constant finding, it probably takes a long time for the sialic acid containing compounds to make their way into the anterior chamber This is not surprising considering the inhibited diffusion of macromolecules in the vitreous It is a question whether it is at all possible for the sialic acid containing compounds to pass the barrier of the cortical tissue layer This may first happen when the molecular sieve function (*Balazs 1961*) of the cortical tissue layer has been destroyed owing to a complete deterioration of the vitreous body an event which probably first takes place at a late stage of tumor growth

It has been surmised *a priori* that the sialic acid containing compound is a glycoprotein Although this seems probable it is by no means certain Only an isolation and identification of the compound or compounds can give the answer

It is evident from the results presented here that the determination of the concentration of sialic acid in the aqueous humor is of no value in the routine diagnosis of malignant melanoma of the choroid Only in special cases of long duration and deterioration of the vitreous body it might be helpful

Summary

The concentration of sialic acid and protein has been determined in the aqueous humor and the vitreous of normal and diseased human eyes

The best normal material was obtained when the samples were taken within 1 hour after death Even in this material the concentration of protein in the aqueous is slightly higher than usually stated in the literature

Elevated values of both sialic acid and protein were found in the aqueous humor and vitreous of eyes with haemorrhagic glaucoma It is surmised that a leaking of blood constituents into the ocular fluids may be responsible for this

In eyes with malignant melanoma of the choroid increased concentrations of sialic acid and protein were constantly found in the vitreous In the aqueous the findings were not constant

The appearance of sialic acid containing compounds in the aqueous seem to depend on the size and duration of the malignant growth

It is concluded that the determination of sialic acid in the aqueous humor is only of diagnostic value in special cases of malignant melanoma of the choroid

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From the ophthalmological Clinic of the University of Ghent
(Director Prof Jules François)

THE RABBIT S ELECTRO OCULOGRAM

BY

J FRANCOIS A DE ROUCK C JÖNSAS and D FERNANDEZ SASSO
(Ghent)

Introduction

Since *François Verriest* & *De Rouck* (1956) published the first clinical test based on standing potential the electro oculogram (EOG) was also achieved a scientific importance (*Arden et al* 1962 *François et al* 1965) principally because standing potential (EOG) and action potentials (ERG) develop in different layers of the retina The *a* and *b* waves of the ERG primarily indicate the activity at the receptor and bipolar levels of the retina while the EOG tests mainly the functioning of the pigment epithelium (*Noell* 1952 1953) The fact that the *c* wave of the ERG is generated in the pigment epithelium (*Brown* & *Wiesel* 1961) and that the *c*-wave is affected by drugs altering the standing potential (*Noell* 1953) also supports this view

Furthermore it is known that no light rise in the EOG can be provoked if there is no contact between the pigment epithelium and the receptors as shown by the fact that in clinical (*François et al* 1967) and experimental (*Foulds* 1966) detachment of the retina EOG does not show light rise

There are only a few reports on the effect of dark and light adaptation on the rabbits electro oculogram (EOG) *Heck* & *Papst* (1957) measured the standing potential and found that after 30 min of dark adaptation it rises in light adaptation to a maximum after 20 30 min *Horsten et al* (1963) found a continuous decrease of the standing potential during the first 30 minutes of dark adaptation to about 70 % of the initial value There findings were confirmed

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by *Imai umi et al* (1966) who reported that the amplitude of the EOG not only decreases during dark adaptation but also increases during light adaptation Both the dark through and the light peak time are approximately 15 to 20 minutes

Material and Methods

The animals used in the experiments were 9 pigmented and 3 albino rabbits of both sexes (eneral anesthesia was performed by injecting intravenously Nembutal (30 mg/kg) Local anesthesia was achieved by instillations of Butoxyaminobenzovldiaethylaminoaethanol and tetracaine

The animals were fixed on a board with the head in a clamp After removing of the fur near the canthi two active electrodes of non polarizable silver were put 1 cm from the internal and external canthi and fixed with collodion The earth electrode was fixed at the ear of the animal For registration of the EOG an Alvar Reega encephalograph was used the paper speed was 15 mm/sec and *the time constant of the amplifier 0 3 sec This is considered to be sufficiently* long for EOG recordings based on eye movements of high velocity The light illumination measured in front of the rabbit s eyes was 15 lux under moderate room light conditions

For producing regular eye movements of the same angular extent the method described by *Horsten et al* (1963) has been used A thread was sutured with two stitches into the sclera or the cornea One end of the thread was led via a pulley to an ironweight and the other end was fastened to a counter weight via another pulley An electromagnet was placed below the smaller weight When the current was switched on the electromagnet drew the smaller weight downwards causing the eye to be drawn forward Switching off made the counterweight drew the eye back to its original position In this way it was possible to repeat the same movements of the eye

The EOG was recorded every third minute At first the rabbit was dark adapted for 15 minutes followed by an illumination of 3000 lux* for 12 minutes and finally another dark adaptation of 15 minutes duration

Before the registration the rabbit was adapted to roomlight during one hour (15 lux)

Results

In the nine pigmented rabbits the FOC amplitude showed during the first 15 min of dark adaptation a continuous decrease of the standing potential to

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Lux s measu e l by the Cossen I uxmeter at the level of the Cornea

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Table II

Evolution of the EOG of 5 albino rabbits expressed in μV and measured every third minute

Minutes	Rabbits				
	No I	No II	No III	No IV	No V
0	1063	600	777	812	675
3	1063	525	805	750	625
6	1031	550	694	688	575
9	1000	450	667	[illegible]	550
12	1000	[illegible]	667	594	575
15	1000	400	639	563	500
18	1031	375	556	563	475
21	906	450	556	594	[illegible]
24	906	[illegible]	667	[illegible]	500
27	1031	575	694	656	550
30	1094	[illegible]	805	688	700
33	1188	950	778	688	625
36	1031	[illegible]	805	781	600
39	1031	[illegible]	750	750	575
42	1031	800	[illegible]	750	550

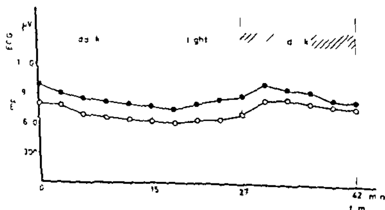


Fig 1

Changes in the EOG amplitude during dark and lightadaptation. Averaged data of nine pigmented rabbits (●-●) and five albino rabbits (O-O) Ordinate amplitude of the EOG expressed in μV. Abscissa time in min.

on average 80 % of the initial amplitude During the three first minutes of the light adaptation period (3000 lux as measured in front of the eye) the EOG showed a decrease before it began to rise reaching in 12 minutes of light adaptation a level on average 92 % of the initial amplitude. During the first minutes of the second dark adaptation period the EOG showed an increase of on average 10 % of the initial amplitude After that the EOG decreased reaching after 15 minutes of dark adaptation an amplitude on average 86 % of the initial one (table I)

The EOG of the five albino rabbits behaved in the same way (table II)

Conclusions and Summary

1 - The standard potential in the rabbit s eye was measured following the technique of *Horsten et al* (1963) for the eye movements and following the method of *François et al* (1966) for the EOG

2 - The modifications of the EOC induced by changes of illumination were st

Table I

Evolution of the EOG of 9 pigmented rabbits expressed in μV and measured every third minute

Minutes	Rabbits								
	No I	No II	No III	No IV	No V	No VI	No VII	No VIII	No IX
0	553	1179	750	929	600	1214	1200	917	1488
3	553	1143	667	893	550	1179	1200	556	1485
6	526	1036	604	893	575	1107	1100	527	[illegible]
9	526	1107	588	929	575	1107	1100	500	[illegible]
12	474	1071	604	786	575	1035	1000	472	1188
15	395	[illegible]	604	786	575	964	1000	500	1125
18	434	928	588	[illegible]	575	929	950	500	1063
21	500	1000	604	714	550	1000	950	556	1155
24	500	1035	625	786	650	964	1100	750	1188
27	558	1107	[illegible]	714	675	[illegible]	1100	750	[illegible]
30	578	1250	771	857	625	1107	1200	[illegible]	[illegible]
33	526	1214	771	892	625	1071	1100	694	[illegible]
36	526	1250	750	964	575	1000	1100	689	[illegible]
39	447	1214	750	928	525	1000	950	611	1188
42	450	1143	750	892	525	1000	950	[illegible]	[illegible]

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Evolution of the EOG of 5 albino rabbits expressed in μV and measured every third minute

Minutes	Rabbits				
	No I	No II	No III	No IV	No V
0	1063	600	777	812	675
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12	1000	425	667	594	575
15	1000	400	639	563	500
18	1031	375	556	563	475
21	906	450	536	594	525
24	906	475	667	695	500
27	1031	575	694	656	550
30	1094	875	805	688	700
33	1188	950	778	688	695
36	1031	875	805	781	600
39	1031	[illegible]	750	750	575
42	1031	800	[illegible]	750	550

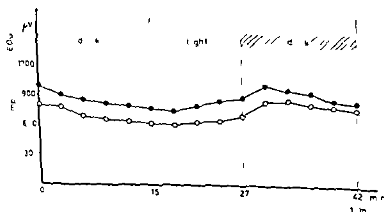


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The EOG of the five albino rabbits behaved in the same way (table II)

Conclusions and Summary

1 - The standard potential in the rabbit s eye was measured following the technique of *Horsten et al* (1963) for the eye movements and following the method of *François et al* (1966) for the EOG

2 - The modifications of the EOG induced by changes of illumination were si

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Minutes	Rabbits								
	No I	No II	No III	No IV	No V	No VI	No VII	No VIII	No IX
0	558	1179	750	929	600	1214	1200	917	1438
3	553	1143	667	893	550	1179	1200	556	1438
6	526	1036	604	893	575	1107	1100	527	1375
9	526	1107	588	929	575	1107	1100	500	1175
12	474	1071	604	786	575	1035	1000	472	1188
15	395	1071	604	786	575	964	1000	500	1125
18	434	978	583	750	575	929	950	500	1063
21	500	1000	604	714	550	1000	950	556	1188
24	500	1035	625	786	650	964	1100	750	1188
27	558	1107	705	714	675	1071	1100	750	1250
30	578	1250	771	857	625	1107	1200	778	1625
33	526	1214	771	892	625	1071	1100	694	1438
36	526	1250	750	964	575	1000	1100	639	1375
39	447	1214	750	928	525	1000	950	611	1188
42	450	1143	750	892	525	1000	950	572	1205

Table II

The results show a great dispersion and more particularly for the absolute amplitude of the EOG (M m m1 m2 m3) This dispers on is much less f r the relative values and especially for *t* the values being here very close The same phenomenon could be observed in man (François et al 1966)

The mean and S values were calculated for all the characteristics for the EOG The results are indicated in table IV

All the differences between the mean values in pigmented and albino rabbits are less than 2 × the standard error so that it may be concluded that these differences are not significant

	Pigmented rabbits			Albino rabbits			Difference of m	Standard error
	m	m + S	m — S	m	m + 2S	m — 2S		
M	975	1166	785	785	925	645	190	119
m_1	731	883	5 9	571	731	411	160	111
d_1	244	68	220	213	243	183	31	19
r_1	0 3	0 52	0 12	0 25	0 31	0 19	0 07	0 11
m_2	994	1115	973	884	1131	730	110	130
l_2	260	34	178	313	431	195	53	[illegible]
r_2	0 32	0 42	0 22	0 61	1 01	0 21	0 29	0 24
m_3	841	1009	673	763	907	619	78	111
d_3	152	2 0	84	121	147	95	31	36
t	136	146	126	150	168	132	14	10

Table III

In the different conditions of illumination the following values can be calculated

- M base value of the EOG the rabbit being adapted to room light
- m_1 minimal amplitude of the EOG during the first period of darkness
- d_1 difference between M and m_1
- r_1 relative drop obtained by dividing the difference d_1 by the base value M
- m_2 maximal amplitude of the EOG induced by light occurring at about the 15th min
- d_2 difference between m_2 and m_1
- r relative increase obtained by dividing the difference d_2 by m_1
- m_3 minimal amplitude of the EOG during the second period of darkness
- d_3 difference between m_2 and m_3
- t Arden Barrada and Kelsey s dark trough given by 100 m_3/m_2

The values we obtained in this way for all the rabbits are shown in table III

	M	m_1	d_1	r_1	m_2	d_2	r_2	m_3	d_3	t
Pigm rabbit n° I	553	395	158	0 20	578	183	0 40	526	52	144 5
Pigm rabbit n° II	1179	928	251	1 20	1250	322	0 30	1143	107	134 6
Pigm rabbit n° III	750	583	167	0 22	771	167	0 28	750	21	130 6
Pigm rabbit n° IV	929	714	215	0 20	964	250	0 30	857	107	135
Pigm rabbit n° V	600	550	50	0 08	675	125	0 20	525	150	123
Pigm rabbit n° VI	1214	929	285	0 20	1107	178	0 10	1000	107	119
Pigm rabbit n° VII	1200	950	250	0 20	1200	250	0 20	950	250	126
Pigm rabbit n° VIII	917	472	445	0 40	778	306	0 60	572	206	165
Pigm rabbit n° IX	1438	1063	375	0 20	1625	562	0 50	1250	375	153
Albino rabbit n° I	1063	906	157	0 10	1188	282	0 30	1031	157	131
Albino rabbit n° II	600	375	225	0 30	950	575	1 50	825	125	187
Albino rabbit n° III	777	539	238	0 30	805	266	0 40	722	83	145
Albino rabbit n° IV	812	563	249	0 30	781	218	0 38	688	93	142
Albino rabbit n° V	675	475	200	0 29	700	225	[illegible]	550	150	149

Table IV

The results sh w a great d spersion and more part cularly for the absolute amplitude of the FOG (M m m1 m2 m) This lispersion is mu h less for the relat ve values and especially for *t* the values being here very close The same phenomenon could I e observed in man (François et al 1966)

The mean and S values were calculated for all the characteristics for the LOC The results are indicated in table IV All the differences between the mean values in pigmented and albino rabbits are less than 2 × the standard error so that it may be con cluded that these differences are not significant

	Pigmented rabbits			Albino rabbits			Difference of m	Standard error
	m	m + 2S	m — 2S	m	m + 2S	m — 2S		
M	975	1166	785	785	9 5	645	190	119
m_1	431	583	5 9	571	731	411	100	111
d_1	244	268	2 0	213	243	183	31	19
r_1	0 32	0 52	0 12	0 25	0 31	0 19	0 07	0 11
m_2	994	1115	973	884	1131	730	110	130
d_2	260	342	178	313	431	195	53	72
r_2	0 32	0 42	0 22	0 61	1 01	0 21	0 29	0 24
m_3	841	1009	673	463	907	619	78	111
d_3	15[illegible]	2 0	84	121	147	95	31	36
t	130	146	1 6	150	169	132	14	10

milar in all rabbits They were rather slow and of slight amplitude The light peak, for instance obtained after 12 min of light adaptation was of nearly the same amplitude as the base value of the EOG in room light adaptation

3 - There was no significant difference in the EOG values between pigmented and albino rabbits The normal mean EOG amplitude was 693 2 ± 310 4 μV

4 - Compared with human beings the standing potential in rabbits changed more slowly and the ratio between the highest and the lowest EOG amplitude was lower (1 3-1 6)

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OCULAR INVOLVEMENT IN LYMPHATIC PARACOCCIDIOIDOMYCOSIS

BY

MAURICIO BRICK M D

Granulomatous lesions in the uvea due to fungus infection are common In dis seminated coccidioidomycosis uveal lesions have been reported and extra ocular involvement is quite frequent in South American Coccidioidomycosis specially on the lids during the initial skin changes [1 2 3]

Uveal and retinal involvement in Paracoccidioidomycosis however does not seem to be frequent as judged from the available literature [4]

The South American Coccidoioides or Paracoccidioides brasiliensis was fully described [5] and differs from the Coccidioides immitis for its smaller size and peculiar way of reproducing by multiple budding like the spokes of a wheel (fig 1) Within human tissues it usually assumes the form of a round body 15 to 30 micra large with double refringent coats Always found in large quanti ties in necrotic areas it is also surrounded by a variable amount of inflamma tory cells (fig 3 and fig 4)

Up to 1950 more than 183 cases of Paracoccidioidomycosis were described 518 of which in the State of Sao Paulo only The disease appears initially at the mucous membrane of the mouth or pharynx very rarely starting from a pulmonary lesion

The initial lesion in the mouth is started by the habit in rural areas of biting or sliking the teeth with grass or any vegetable matter available Through mi ro lesions in the gums palate or even tonsils the Paracoccidioides brasilien sis which is carried by the grass to the mouth reaches the lymphatic spaces for which it shows a special predilection

Necrotic lesions of the skin surrounding the mouth may occur Many times

R ceived J nuary th 1969



Fig 1 (Brick)
Paracoccidioides brasiliensis A large organism is shown at the centre of the photograph with its double refringent coat and three spoke like structures found during reproduction (enlarged photo) (Hematoxylin and eosin X 240)

such lesions spread up to the lids involving the eye from outside The disease affects mainly the lymph nodes and progresses through the lymph vessels At the early stages the neck nodes are involved showing enlargement and necrosis Very often they fistulize giving way to a caseous material in which the fungus is easily identified Advanced stages show general lymphatic involvement and blood current metastasis In many cases blood cultures succeed in growing Paracoccidioides

The present case was seen at the University Hospital in 1963 with generalized Paracoccidioidomycosis and eye involvement

Case History

J R S a 28 year old mestiço man was admitted to the Department of Infectious and Parasitic Diseases of the University Hospital in June 1963 He had been to another hospital previously and was submitted to abdominal operations twice His main symptoms have been vomiting and jaundiness Two fistulizing nodes in the neck were reported and the diagnosis of Paracoccidioidomycosis



Fig [illegible] (Brick)

Low power view of pericoledocian lymph node removed during surgery A large necrotic area occupies almost all of the preparation (Hematoxylin and eosin X [illegible]4)

was established from examinations of the fistulizing material Five months prior to admission the patient noticed loss of sight on the right eye

On admission the patient complained from digestive troubles and general asthenia A severe jaundiness was noticed and vision on the right eye was finger counting at 2 meters

Laboratory tests revealed extreme liver insufficiency with high levels of cholesterol and alkalin phosphatase Hyperglycemic crisis followed each intravenous administration of glucosated serum Treatment with Prednisone and Amphotericin B was instituted and the patient was transferred to Surgery to further exploration

He was then submitted to addominal surgery and on that occasion a complete removal of the pericoledocian nodes was performed for they were found to be extremely enlarged and involved in an inflammatory mass thus explaining the



Fig 3 (Brick)
Necrotic area of lymph node where several Paracoccidioides can be identified (Hematoxylin and eosin × 60)

clinical findings A biopsy of the liver was also done and the coledocian duct was freed

After three weeks the patient returned to the Parasitic and Infectious wards and we were able to see him again The pathologic examination of the peri coledocian nodes showed an extreme degree of inflammatory changes The nodes were enlarged necrotic and calcified Large quantities of Paracoccidioides brasiliensis were found within the necrotic and caseous areas (fig 2 3 and 4) The liver biopsy only revealed a high degree of stasis

The left eye was normal The right eye showed at that time vision of fingers at 1 5 meters No abnormalities were found in the anterior segment The lens and anterior vitreous were clear The posterior vitreous was somehow cloudy but still allowing examination of fundus details The posterior pole was occupied by a large yellowish mass with blurred margins The disk was pale and showed some degree of neo vascularization arising from its upper margin (fig 5)

The whole periphery of the fundus was also involved Every retinal vessel was enclosed by multiple exsudates as in periphlebitis which spread to the neighbour structures (fig 6)

The eye involvement was thought to be originated from the retinal and choroidal vessels The treatment was left in charge of the Parasitic and Infectious

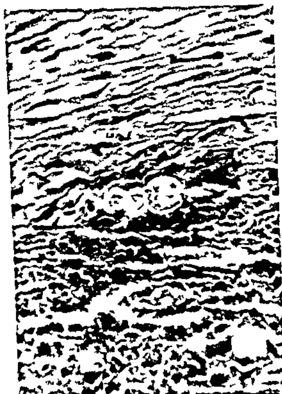


Fig 4 (Brick)

H gh power view of necrotic area seen in figure 3 Three organisms occupy the centre and several other are scattered Intense necrosis and destruction of tissue pattern can be seen involving the organisms

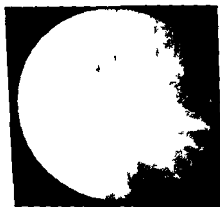


Fig 5 (Brick)

Fund s ppearance of ight eye The d sk is blurred by posterior vitreous exsudation. Retinal vessels are involved by patches of inflammatory material

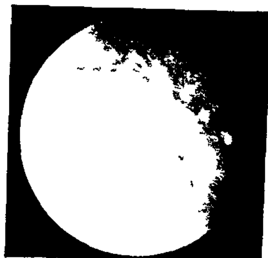


Fig 6 (Brick)

Peripheral view of the right eye fundus Both the superior artery and vein are enclosed and surrounded by exsudative patches The bottom which corresponds to the posterior pole is blurred by vitreous opacities

Diseases Department and after four weeks the patient left the Hospital with an appointment to return to the Eye Department within a month As he failed to do this his contact was lost

Conclusions

A probable blood stream spread explains the retinal and choroidal involvement in the present case Such involvement is found in other sistemic mycosis and occurs only in cases were involvement is massive and of long duration

Summary

A case of Paracoccidioidomycosis of the lymphatic system affecting the nodes of the neck and the ileo hepatic system is presented There was mechanical compression and inflammatory involvement of the coledocian ducts and liver stasis consequently The neck nodes were fistulizing during some time and the diagnosis of Paracoccidioides brasiliensis mycosis was established after the parasit was found within the caseous material from such nodes Besides general symptoms the patient complained of loss of vision of the right eye which

showed involvement of the retinal and choroidal vessels and a large and dense mass of exsudation occupying the posterior pole. The abdominal nodes removed surgically revealed the typical involvement and organisms

Acknowledgements

I wish to thank
1) Dr Carlos Cesar Ferreira and
2) Dr Acyr Mulinari
Who helped me in preparing the fundus pictures and the photomicrographs

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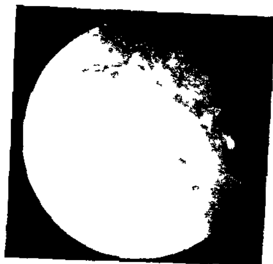


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Department of Anesthesiology
Indiana University Medical Center Indianapolis Indiana

RETROBULBAR BLOCK FOR OCULOCARDIAC REFLEX DURATION OF PROTECTION BY COMMON LOCAL ANESTHETICS

BY

RAY J DEFALQUE M D

Introduction

There exists sound evidence that a successful retrobulbar block effectively prevents the oculocardiac reflex under general anesthesia[1 2] Lidocaine is most commonly used for this block but situations may occur which *preclude its use* (allergy longer operations) It thus seems useful to know the duration of protection offered by other local anesthetics

The acquisition of such data presents three difficulties

1 Because the series of drugs must be compared in the same subject humans cannot be used However animal data on local anesthetics must be transposed to man only with the greatest caution[3]

2 The oculocardiac reflex is erratic[1] and cannot be systematically reproduced under standard conditions This rules out the electrocardiogram to measure effective blockade of the reflex afferent fibers

3 Since the latter have been identified as either the parasympathetic short ciliary fibers[4] or the trigeminal sensory long ciliary nerves[1] both pathways must be investigated simultaneously

Received January 20th 1969

Method

Complete reserpinization of the awake dog produces miosis by central and peripheral sympathetic denervation[5] Pinpoint miosis then occurs if one suppresses the afferent cortical stimuli by light barbiturate sleep[6] but the corneal reflex persists In such dogs a retrobulbar block paralyzing ciliary nerves and ganglion dilates the pupil to a 6 mm resting diameter[6, 7] and produces corneal anesthesia Corneal reflex and maximum miosis return when the anesthetic wears off and both parameters thus measure the duration of blockade

Twelve dogs (12 18 kgs) with normal eyes received 0 5 mg/kg Serpasil® intravenously once a day for three days Then under 30 mg/kg pentobarbital an 18G needle was introduced into each retrobulbar space from the inferior temporal margin[6] Once the space had been identified (mydriasis with 2 ml of a local anesthetic) 0 5 cm of a Portex® epidural catheter was inserted Its external extremity was sutured to the skin after the needle had been removed

Each of the following days one of eleven local anesthetics was injected in both eyes in random order Each series was completed within two and a half weeks while the animal was still fully reserpinized Before the test and every hour thereafter the animal received 2 mg/kg secobartital intravenously Two and a half ml of the studied local anesthetic was injected slowly at a constant rate of 0 5 ml/second via the retrobulbar catheter

Corneal reflex and pupillary size were checked every minute up to the maximum response then every five minutes until miosis began at which time the one minute schedule was resumed The corneal reflex was tested by gently stroking the four corneal quadrants with a dog eyelash mounted on a pencil The apparent pupillary diameter was measured with a millimeter graduated plastic ruler placed one mm before the pupillary center

The eleven local anesthetics tested were Procaine 1 % chlorprocaine 1 % piperocaine 1 % lidocaine 1 % propitocaine 1 % mepivacaine 1 % propoxycaine 1 5 % hexylcaine 1 % tetracaine 0 15 % dibucaine 0 02 % and bupivacaine 0 25 % Buffered commerical solutions were used except for dibucaine (commercial 1 200 spinal solution diluted 10 times in normal saline buffered at pH [illegible] 0)

Results

Miosis and corneal reflex disappeared and returned practically simultaneously and thus could be integrated as one parameter

For each drug we calculated the means of *latency* and duration for both eyes of each dog then the means for the twelve dogs These last values and their standard deviation are presented in the table and figures

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Table 1

Latency and duration of protection by local anesthetics Means and (Standard Deviations) in minutes

Drug	Latency	Duration of Protection
Procaine 1 %	1¾ (± ½) min	62 (± 7) min
Chlorprocaine 1 %	1 (± ½) min	70 (± 4) min
Piperocaine 1 %	1¼ (± ½) min	[illegible]8 (± [illegible]) min
Lidocaine 1 %	¾ (± 1/) min	85 (± 8) min
Propitocaine 1 %	1¾ (± ¾) min	105 (± 5) min
Mepivacaine 1 %	1 (± ½) min	120 (± 9) min
Propoxycaine 0 5 %	2 (± ½) min	116 (± 1[illegible]) min
Hexylcaine 1 %	2¼ (± 1¼) min	125 (± 8) min
Tetracaine 0 15 %	3¾ (± ¾) min	152 (± 22) min
Dibucaine 0 02 %	4 (± 1) min	203 (± 10) min
Bupivacaine 0 25 %	2¼ (± 1/) min	220 (± 1[illegible]) min

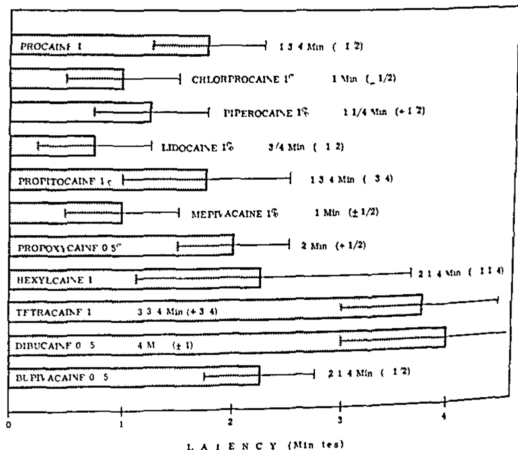


Fig 1

Latency of 11 local anesthetics in minutes Means of 12 dogs with their standard deviations

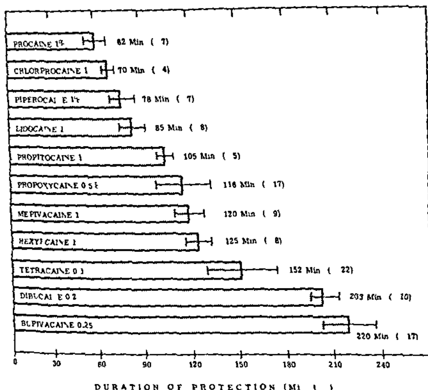


Fig 2

Duration of protection by 11 local anesthetics in minutes Means of 12 dogs with their standard deviations

Discussion

This experimental design seems to overcome the objections presented in the introduction

It was gratifying to see miosis and corneal reflex disappear and return almost simultaneously though they are controlled by different structures This identical blocking pattern may be due to the anatomic similarity of the retrobulbar fibers[9]

In theory barbiturates and reserpine might increase the duration of the nerve blockade but the literature offers no evidence of such potentiation[10]

There is ample evidence that the oculocardiac reflex is relatively harmless and certainly does not cause cardiac arrest while the retrobulbar block is not free of complications We by no means recommend routine preoperative retrobulbar block but only suggest that other local anesthetics may at times prove superior to lidocaine

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Lidocaine 1 %	¾ (± ½) min	85 (± 8) min
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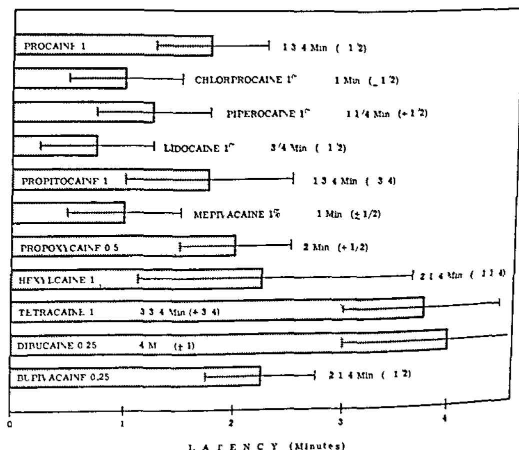


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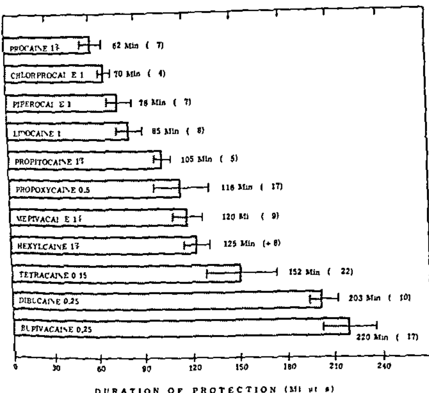


Fig 2

Duration of protection by 11 local anesthetics in minutes Means of 12 dogs with their standard deviations

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Summary

The latency and duration of miosis and corneal anesthesia after retrobulbar injection of eleven different local anesthetics were studied in twelve reserpinized dogs under light secobarbital sleep in an attempt to estimate the duration of protection against the oculocardiac reflex offered by these drugs when injected retrobulbarly in clinical practice

The eleven local anesthetics (with their average duration of protection) were procaine 1 % (62 min) chlorprocaine 1 % (70 min) piperocaine 1 % (78 min) lidocaine 1 % (85 min) propitocaine 1 % (105 min) mepivacaine 1 % (120 min) propoxycaine 1 5 % (116 min) hexycaine 1 % (125 min) tetracaine 0 15 % (152 min) dibucaine 0 02 % (203 min) bupivacaine 0 25 % (220 min)

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DIVIDED NEVUS

BY

NIELS EHLERS

The term "divided nevus", or in German Geteilte Naevus was proposed in 1919 by *A Fuchs* to designate the simultaneous occurrence of nevi on opposing parts of the upper and the lower lids The two nevi form a unit when the lids are closed and are divided when the eye is opened Fuchs reported six cases of this peculiar disease Two cases had previously been described by *von Michel* (1908) and cases have later been reported by *Bachstez* (1923) *Bardelli* (1935) *Collenza* (1937) *Callahan* (1946) *Fuchs* (1950 1960) *Lo* (1951) *Cunningham* (1952) *Harrison & Okun* (1960) *Heydenreich* (1960) *Collier* (1964) and *Ehlers* (1965) A total of 25 cases has been described

Clinical Appearance and Course

Divided nevi appear as tumours on the opposing margins of the upper and the lower lids They are localized to the middle of the lids or around the medial or lateral canthus The size varies from hardly visible to great disfiguring tumours which can be level with the skin (case 6 below *Collier* 1964) be pedunculate (case 8 below) or most frequently be slightly protruding (case 1 be

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low) Sometimes larger parts of the surrounding skin are included (cases 4 & 9 below) but rarely and only late conjunctiva Bilateral cases have not been observed

The degree of pigmentation may vary and a nevus need not be more pigmented than the surrounding skin. Cilia are often present and these are said to be greater than normal (*Fuchs* 1950)

Most often the tumours are observed immediately after birth but the first appearance may be in senescence (case 7 below) The tumours generally show a slow growth which may however stop at any age

The cases reported below illustrate the clinical picture and the course of the disease

Case 1 (Radiumstationen Arhus 579/56) A 33 year old man who since his birth had had pigmented nevi on the left upper and lower lids An examination during his 21st year unveiled a 15 × 7 mm large nevus protruding about 5 mm on the margin of palpebra superior and a 10 × 7 mm large nevus protruding about 3 mm on palpebra inferior (Figs 1 and 2) The tumour of the lower lid contained a 2 × 3 mm area of black pigmentation. The tumour of the upper lid had been growing slowly till the examination. Visual acuity and ophthalmoscopy was normal

When he was 33 years old an examination unveiled on palpebra superior a 18 × 10 mm papillomatous hairy tumour stretching 1 2 mm into conjunctiva with a 3 × 3 mm dark pigmented area centrally The tumour on palpebra inferior measured 8 × 8 mm was hairy and stretched slightly into the conjunctiva Apart from slight lacrimation the patient suffered no discomfort Treatment was not found indicated Biopsy was not taken.

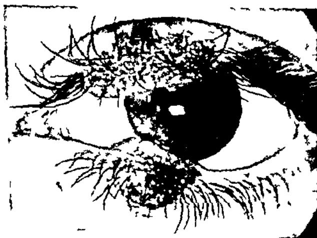


Fig 1
Case 1

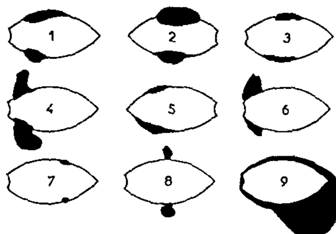


Fig 2
Diagram of the reported cases The numbers refer to the corresponding case reports

Case 2 (Radiumstationen Århus 309/58 A 47 year old man who has from his birth had well defined tumours opposite each other in the middle of the right upper and lower lids During recent years slow growth A protruding verrucose excrescence was found on palpebra superior covering part of bulbus (Fig 2), overgrown with cilia bristling in all directions Conjunctiva was not included A similar rather smaller tumour was seen on palpebra inferior Biopsy taken from the tumour on the upper lid showed intradermal nevus with no junctional activity Examination of the eyes showed normal conditions just as the other objective examinations showed nothing abnormal

Case 3 (Department of Ophthalmology Rigshospitalet Blegdamsvej Copenhagen 1731/64 65) A 50 year old man who has from his birth had two small brown flecks centrally on the left upper and lower lids where the cilia quickly grew large From the age of 20 hampered by recurring hordeola The tumours thickened but have later remained totally unchanged At the age of 15 treated with CO freezing and diathermy coagulation without effect Now thickening of the central halves of upper and lower lids was found (Fig 2) The surface was irregularly rugged with varying pigmentation and irregular cilia Examination of the eyes showed normal conditions At the right commissure of the lips a 2 × 3 cm large café au lait spot showed No indication for treatment or biopsy

Case 4 (Department of Plastic Surgery Rigshospitalet Blegdamsvej Copenhagen 551) A 22 year old man who from his birth had had hairy nevi on the left upper and lower lids which have not grown Apart from slight lacrimation no discomfort At the age of twenty were found extended nevi on the medial third of upper and lower lids not including conjunctiva (Figs 2 and 3) Upper lachrymal point preserved lower not to be localized On the front and the back of thorax were found some smaller pigmented nevi The tumours on the lids were excised The defects were covered with rotary pieces from lateral parts of the lid and with free full skin grafts from the left retroauricular region Microscopy of both tumours showed nevus of junction type



Fig 3
Case 4



Fig 4
Case 9

Case 5 (Department of Ophthalmology Kommunehospitalet Copenhagen 196?) An 18 year old woman who from her birth had had nevi on the right upper and lower lids Treated with CO freezing with no effect On the lower lid was now found a 20 × 8 mm large somewhat protruding nevus and on the upper a rather smaller one (Fig 2) No indication for treatment or biopsy

Case 6 (Department of Plastic Surgery Rigshospitalet, Blegdamsvej Copenhagen) A 5 year old girl who from her birth had had brown pigmented non protruding nevi medially on the left upper and lower lids (Fig ?) No indication for treatment or biopsy

Case (Laboratory of Ophthal path Copenhagen 706/68) A 73 year old woman who durirg the latest 4 ꜟ years had noticed two smaller tumours opposite each other on the marg n f the left upper and lower lids (Fig 2) now nearly the size of a pea solid and smooth Both were removed by simple excision Micrcscopy of both showed nevus intradermalis

Case 8 (Department of Ophthalmology Rigshospitalet Blegdamsvej Copenhagen 1998 64 (5 recorded by the author in 196) A 58 year old woman who from her birth had had two small welldefined tumours opposing each other on the margins of the left upper and lower lids The tumours had grown slowly Now was found two pedunculate cth ted tumours the size of a hazelnut on the margins of the upper and lower lids (F g ?) Conjunctiva was not included Traction ectropion of the lower lid caused by the weight of the tumour was f und Otherwise examination of the eyes showed nor mal conditi ns No sk n tumours or cafe au lait spots Both tumours were removed through simple excis on Microscopy of both showed nevus intradermalis

Ca 9 (Department of Plastic Surgery Rigshospitalet Blegdamsvej Copenhagen ?98/ ( ) A 16 year old girl who from her birth had had large nevus round left eye includ ing both l ds and stretching upwards of 4 cm into the cheek (Figs 2 and 4) Nevus

substantially pigmented and hairy The tumour tissue was removed through several excisions and replaced by free skin grafts An ectropion occured which could later be corrected No subjective discomfort now The lower lachrymal duct disconnected 5 mm from the lachrymal point Microscopic diagnosis nevus with junctional activity

Occurrence and Incidence

Divided nevi are most frequently recorded among white people, but it has been stated that they are found frequently among the Chinese where six cases are recorded (*Fuchs* 1950 *Lo* 1951) No cases seem to have been observed among black people

Divided nevi have been considered extremely rare In the present study it has been possible among 5 million inhabitants to find nine cases during a 10 year period This seems to be many seeing that in the ophthalmological literature since the change of the century only some 25 cases are recorded The reason is presumably that the condition has been shown no interest During the period 1915 1955 *Pers* (1967) found at examinations of giant nevi several cases resembling case 9 of the present study Another possibilly is that divided nevi and perhaps nevi generally speaking are far more frequent among blond Scandinavians There are however no records of divided nevi from the other Scandinavian countries

Familial cases are not known with any certainty yet the patient of cases 8 of the present study has stated that she has a sister with tumours on upper and lower lids too It has proved impossible to obtain further informations

Differential Diagnosis

Any process attacking the margin of the lid may of course affect upper and lower lids simultaneously but only rarely will a real differential diagnostic problem exist

Melanomas may look like nevi and frequently only microscopy will make the differential diagnosis feasible Some melanomas occur in nevi Among divided nevi however malign transformation has been observed in only one case (*Fuchs* 1950) after surgical treatment Divided melanomas have not been mentioned in the literature Likewise neurofibromas may look like nevi In case 8 recorded here the clinical diagnosis was neurofibromatosis Isolated presence of neurofibromas opposing each other on the upper and lower lids have not been found recorded Epitheliomas from epidermis or the glandular structures of lid margin may seem a possibility even if these will often

display ulceration and are apparently not recorded opposite each other on the upper and lower lids Existence from birth and hairiness suggest nevus

It seems feasible that infectious processes cause contact infection on the other lid Papillomas seem a possibility and from earlier days we have records of syphilides and tuberculomas opposing each other on the upper and lower lids

Treatment

Many cases have not been treated and fear of inducing malign transformation has served as a warning (*Fuchs* 1950 60) This fear however seems less well founded (*Stegmaier* 1961) Operative treatment is possible even if difficult dilatory and frequently requiring several operations

A pedunculate or a small protruding tumour can easily be excised (cases 7 and 8 above) Removal of larger tumours has been described by *Collan a* (1937) and *Callahan* (1946) and has been made in cases 4 and 9 above

Callahan excised the tumours and covered the defect with one skin graft thus creating a temporary tarsorrhaphy In a later operation skin from the eyebrows was implanted as a substitute for the lashes After 2 months the lids were divided In cases 4 and 9 above the tumours were excised and the defects covered with free skin grafts without the formation of a temporary tarsorrhaphy A similar procedure was described by *Collen a* (1937)

Freezing with CO_2 or coagulation have been attempted rather unsuccessfully (cases 3 and 5 above) Nevi are radioresistent

Histopathology

Microscopic examination has most frequently shown typical nevi of intradermal type with nests and strands of nevus cells separated from the overlying epithelium The amount of pigmentation has been varying Only few cases (*Harrison & Okun* 1960 cases 4 and 9 above) have shown junctional *activity* i e nevus cells at epidermal dermal junction Junctional nevi have been considered more likely to undergo malignant transformation However *by serial* sections junctional activity may be demonstrated in the majority of nevi (*Stegmaier* 1961) and in eyelid nevi *Reese* (1963) found it in 90 % It appears that a nevus has a life cycle of growth rest involution and sometimes spontaneous disappearance thus young nevi are likely to show junctional activity while older nevi are more probably of the intradermal type This is in good accordance with the preponderance of intradermal nevi among the divided nevi

which start their life before birth, and are elevated and hairy at the time of delivery

Histologic difference between nevus of the upper and lower lids has never been demonstrated

Pathogenesis

The nevus cells originate from melanoblasts or from Schwann s cells (*Reese* 1963), both having neuroectodermal origin

Already *Fuchs* (1919) proposed that nevi develop while the lids are joined during foetal life This explains the juxtaposition of these tumours The lids of the foetus join at the 38 40 mm stage (about the 9th 10th week) and open by a complicated process beginning about the 100 mm stage (about 15th week) with lipid development in the junctional epithelium (*Andersen Ehlers & Matthiessen* 1965) The junction is exclusively epithelial connective tissue does not grow from one lid into the other Thus divided nevi are of general interest for the nevus pathogenesis showing that nevi arise early in foetal life presumably be tween the 9th and the 15th week The above mentioned case 7 where nevi were not observed till the age of 70 does not contravene the pathogenesis as nevus cells can be presumed to lie latent in the tissue for a long time This concep tion of the pathogenesis also finds support in the fact that only nevi occur divided

The common rather frequently occurring palpebral nevi most frequently arise after puberty while divided nevi are practically always present at birth One possibility is that divided nevi are caused by invasion of melanoblasts ori ginally destined for the choroid

Summary

The term divided nevus denotes simultaneous occurrence of nevi on opposing parts of upper and lower lids 24 cases from the literature are reviewed and 9 cases presented The clinical appearance course occurrence and frequency differential diagnosis treatment histopathology and pathogenesis are discused The 9 cases observed in Denmark during a 10 year period show that the condi tion is more common that generally stated

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Addendum

After this paper was finished an additional case has been observed

Case 10 (Department of Ophthalmology Kommunehospitalet Århus) A 75 year old woman who from birth had had a small tumour on the right lower lid measuring 3 × 3 mm No change in size had been noted The tumour was non pigmented but on its anterior margin a small pigmented spot was seen. On the opposing part of the upper lid a similar small pigmented area occurred *The cilia were normal* Treatment was not found indicated

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OCULAR SYMPTOMS IN SACCULAR ANEURYSMS OF THE INTERNAL CAROTID ARTERY

(A Survey of 100 Cases)

BY

RUTH RIISE

Introduction

During the past two decades more and more exact definitions of the clinical manifestations of intracranial aneurysms have been given

Ophthalmologists must be aware of the neuro ophthalmologic symptoms of intracranial aneurysms which according to *Dandy* (1944) are localized mostly in the internal carotid artery and involving the oculomotor, the trochlear, the abducens the optic and the trigeminal nerves

In a review of the clinical findings in ophthalmoplegia *Godtfredsen* (1963) showed that 30 35 % of patients with ophthalmoplegia had an intracranial aneurysm

According to their localization in relation to the anterior clinoid process the internal carotid aneurysms are classified under supraclinoid and infraclinoid aneurysms The supraclinoid group comprises mainly aneurysms located at the origin of the posterior communicating artery whilst the infraclinoid aneurysms are located within the cavernous sinus This is an appropriate grouping since both symptomatology and treatment differ in the two groups

A study of 102 intracranial aneurysms published by *Henderson* in 1955

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Fig I
Supraclinoid internal carotid aneurysm



Fig II
Infraclinoid internal carotid aneurysm

showed that 35 of the 40 internal carotid aneurysms found were supraclinoid and 5 were infraclinoid

In most cases the primary symptoms in supraclinoid aneurysms will be splitting headache and stiffness of the neck caused by a subarachnoid bleeding Papilloedema and haemorrhage of the fundus are then frequent findings (*P Rasmussen* (1965) Associated with these symptoms there will often be partial or total oculomotor palsy Less frequently trochlear and abducens palsy will occur In cases without subarachnoid haemorrhage the most frequent finding will be oculomotor palsy often appearing as a slight ptosis subsequently developing into palsy of the ocular muscles and pupillary changes (*Henderson* (1955))

Subarachnoid bleeding is a rare occurrence in infraclinoid carotid aneurysms As these aneurysms are usually large they are frequently associated with exophthalmos Oculomotor palsy is a frequent finding and in most cases it is associated with trochlear and abducens palsy (*Henderson* 1955)) The corneal sensitivity will often be reduced in consequence of the lesion of the trigeminal nerve (*Jefferson* (1938 *Bonnet* (1955) *Meadows* (1959) *Jaeger* (1950))

Blurring of vision or visual field defects – most often homonymous – caused by the optic nerve lesion compression of the optic chiasm or lesion of the optic tract will occur in both supraclinoid and infraclinoid aneurysms (*Wilbrand & Saenger* (1900) *Jefferson* (1937 and 1955) *Walsh* (1964))

Furthermore in either group of patients the presenting signs of the aneurysm will frequently be of an ocular nature Hence *Zielinski* (1957) found that 48 % of patients with saccular aneurysms of the internal carotid artery complained primarily of ocular symptoms

Most of the patients have headache frequently as facial pain and in some cases located in the eye (*P Rasmussen* (1965))

Because of more exact roentgenologic diagnosis and improved surgical methods the prognosis in aneurysms have become much more favourable during recent years Early operation provides the best results (*Botterell et al* (1962) *Henry Troupp et al* (1958)) Following surgery the ophthalmoplegia will often improve although on rare occasions only it disappears completely A slight ptosis and in some cases slight dilatation of the pupil will remain but usually these symptoms do not give rise to any complaints (*Heppler & Cantu* (1967))

Own material

As regards all patients admitted to the Department of Neurosurgery G Århus Municipal Hospital over the period from April 1st 1943 to March 31st 1965 with a diagnosis of saccular aneurysm of the internal carotid artery the records were reviewed with respect to the ocular symptoms

During the above period 201 patients were admitted with saccular intracranial aneurysms In 108 cases the aneurysm was located on the internal caro

tid artery Eight patients were excluded because it was impossible to undertake an ophthalmologic examination

Primarily the location of the aneurysm was determined by arteriography Only patients with a positive arteriographic diagnosis were operated on Generally the findings at arteriography surgery and in some cases at autopsy showed good concurrence

General data

Sex

Males	Females
38	62

The preponderance of females as regards internal carotid aneurysms agrees with the figures given by *Henderson* When intracranial aneurysms are viewed collectively the sex incidence is almost equal

Age

< 40 years	40 60 years	> 60 years
34	53	13

The average age is low but the spreading is appreciable (12 74 years)

Location

Supraclinoid	Infraclinoid
9	8
Right side	**Left side**
51	49

It will be seen that by far the greater number of internal carotid aneurysms were supraclinoid which corresponds to the findings of previous authors (*Dandy* (1944) *Henderson* (1955))

Number of aneurysms

One	Multiple
91	9

In addition to the internal carotid aneurysms one or more aneurysms were found on one of the intracranial vessels in 9 cases However, in all these cases the symptoms could be ascribed most likely to the aneurysm found on the internal carotid artery

In the majority of patients the blood pressure recorded on admission was normal Subarachnoid haemorrhage occurred both in patients with high blood pressure and with normal blood pressure

Blood pressure

Diastolic blood pressure	With subarachnoid haemorrhage	Without subarachnoid haemorrhage	Total
> 100	11	2	13
< 100	64	21	85
Not stated	2	0	2
Total	77	23	100

Complaints

The most frequent complaint in patients with saccular internal carotid aneurysms was headache This symptom was reported by 95 patients In most cases there was a dull frontal headache In 11 patients the pains were located in the eye on the side of the aneurysm Headache not associated with rupture of the aneurysm or eye symptoms was reported in 9 cases Headache assiciated with eye symptoms and without clinical signs of rupture of the aneurysm occurred in 16 cases In these cases the symptoms might indicate growth of the aneurysm In 70 cases the headache developed in connection with rupture of the aneurysm and in these cases the pain occurred suddenly and was violent

Forty eight patients were suffering from ocular complaints on admission and in 19 patients the symptoms were not related to a rupture of the aneurysm In 11 of the patients the symptoms had persisted for more than 12 months in two of them the period was between 6 and 12 months whilst the remaining 35 patients had had the symptoms for less than 6 months In more than 50 % of the cases the symptom was diplopia Some of the patients complained of ptosis Blurring of vision was a rare complaint as compared with the findings at the objective examination

In 52 patients without primary ocular symptoms the presenting finding was most often subarachnoid bleeding this symptom being present in 46 of these patients Of the remaining 6 patients the cause of admission in 5 cases was headache and mental disturbances in one

Objective findings

The objective findings at ocular examination on admission showed a domination of oculomotor palsy This symptom was found in 39 cases and in 29 of these total palsy (involving all branches) was observed In the majority of cases the palsy had commenced as a slight ptosis and had then developed over days weeks or months into total palsy Most frequently a rapid development of this symptom was associated with subarachnoid haemorrhage (in 26 of the 39 patients suffering from oculomotor palsy subarachnoid bleeding was present) Of the 10 cases with partial oculomotor palsy ptosis was recorded in 9 cases palsy of the superior rectus muscle in 7 cases palsy of the sphincter of the pupil in 6 cases and palsy of the medial rectus muscle in 4 cases

Trochlear and abducens palsy and lesion of the trigeminal nerve (reduced corneal sensivity) occurred mainly in infraclinoid aneurysms

Exophthalmos was found in one case only in connection with infraclinoid aneurysm The protrusion was only moderate

Visual field defects were recorded in four cases associated with supraclinoid aneurysms The defects appeared mainly as homonymous hemianopsia

Papilloedema was observed in 18 cases – in connection with subarachnoid bleeding exclusively The associated haemorrhages were mainly streaky and of a peripapillary location In a few cases there was pre retinal bleeding

In 39 cases (38 supraclinoid and 1 infraclinoid) the visual acuity was not tested because of poor general condition The group blurring of vision comprises patients with $< 6/9$ on the defective eye

Most likely the occurrence of palsy of the ocular muscles visual field defect and reduced corneal sensitivity is much higher than that demonstrated in our material since many of the patients with subarachnoid bleeding were too weak to undergo a thorough examination

100 cases of saccular aneurysms of the internal carotid artery

ocular symptoms	92 supraclinoid	8 infraclinoid	100 total
Oculomotor palsy	34	5	39 (26)
Trochlear palsy	0	1	1 (0)
Abducens palsy	1	4	5 (1)
Reduced corneal sensitivity	4	2	6 (3)
Exophthalmos	0	1	1 (0)
Visual field defect	4	0	4 (4)
Papilloedema	18	0	18 (18)
Optic atrophia	5	1	6 (2)
Haemorrhage	19	0	19 (19)
Blurring of vision	16	1	17 (10)

(The figure in the brackets indicate the number of subarachnoid bleedings)

Sixty eight patients underwent surgery In cases of supraclinoid aneurysms ligation of the aneurysm combined if necessary with muscle wrapping was conducted As regards infraclinoid aneurysms ligation of the carotid artery was carried out in the neck on the same side as the aneurysm

Thirty two patients died in hospital and a further 8 patients died within one year after discharge In 13 of the 40 patients who died ocular symptoms were the presenting sign whereas in 27 patients other presenting symptoms were observed (mainly subarachnoid haemorrhage) Hence the prognosis seems to be most favourable if the primary symptoms of the aneurysm are of an ocular nature and in particular if the patient is admitted to hospital before the occurrence of subarachnoid bleeding

Thirty five of the 48 patients who complained of ocular symptoms were still alive after one year A written inquiry to these patients concerning inter alia the presence of ocular symptoms produced the following results

Subjective ocular symptoms after one year

	Improved	Unchanged	Worse	Total
With surgery	23	5	0	28
Without surgery	3	3	1	7
Total	26 (18)	8 (4)	1 (0)	35 ([illegible])

(The figures in brackets indicate the number of subarachnoid haemorrhages)

Conclusion

The internal carotid artery is the most frequent location for saccular intra cranial aneurysms (approximately 50 %) Aneurysms at this location will most often be associated with ocular symptoms The ocular symptoms are determined by the anatomical conditions because the internal carotid artery throughout its course is closely related to the oculomotor the trochlear the adducens the trigeminal and the optic nerves The incidence of saccular carotid internal aneurysms is highest among females in the age group from 40 60 years The most frequent location is supraclinoid (92 %)

The majority of patients complain of headache The presenting ocular symp toms are ptosis and diplopia as a result of oculomotor palsy which is present in 39 % of the cases Abducens palsy and lesion of the trigeminal nerve occur mostly in connection with infraclinoid aneurysms Trochlear palsy exophthal mos visual field defect blurring of vision and papillary atrophy are rare symptoms

Headache and ocular symptoms occur most frequently in connection with subarachnoid bleeding However 19 % of the patients presented ocular symp toms without subarachnoid bleeding In cases without rupture of the aneurysm headache and ocular symptoms might indicate growth of the aneurysm

After surgery most of the patients report improvement of the ocular symp toms The prognosis is best in cases where the aneurysm is diagnosed and treated before rupture occurs

Summary

We have reviewed the records of 100 patients in whom saccular aneurysm of the internal carotid artery had been diagnosed and who were admitted to the Department of Neurosurgery over a period of 22 years with a view to ocular symptoms These symptoms are related partly to the location of the aneurysm and partly to the occurrence of subarachnoid bleeding

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RETRACTION SYNDROME OF DUANE ASSOCIATED WITH MYASTHENIA GRAVIS

BY

O P SHARMA M S and V P S TOMAR M S F I C S

In 1905 Alexander Duane collected 54 cases of limitation or absence of abduction and weakness of adduction of one or both eyes associated with retraction of the affected eye on adduction narrowing of the palpebral fissure of the affected eye on adduction and tendency to widening on abduction and described in detail 14 cases of his own Earlier reports of this syndrome named after Duane had come from Sinclair[19] and Friedenwald[6] Since then the number of recorded cases has been increasing – Danis[3] collected and analysed 229 cases – and interesting cases are being added to the literature

The mechanism of the anomaly is variable as all cases do not have the same aetiology (Duke Elder[5]) Gifford[7] remarked upon their possible relationship to *birth injury* The left eye is affected more commonly than the right (Aebli[1]) and about 10 20 % cases are bilateral (Danis[3]) Females are more *frequently* affected than males (Walsh[12]) A hereditary tendency has been noted although 90 % cases are sporadic (Duke Elder[5])

The syndrome has been found in association with other ocular *defects such* as keratoconus microphthalmos (Waardenburg[11] Bietti[2]) as well as in association with deformities elsewhere in the body such as facial palsy facial asymmetry Klippel Feil *synostosis* (Pintucci & Tizio[8]) cervical spina bifida and labyrinthine deafness (Wildervanck[13]) Walsh[12] has quoted a case of Duane s syndrome which was in combination with either a peroneal muscular atrophy or a muscular dystrophy *Recently* Regenbogen & Stein[9] have described a case of syndrome of crocodile tears associated with Duane s syndrome

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Fi~ 3
Abduction of left eye – wideming of palpebral fissure.

Convergence pupillary reactions and fundi were normal. Vision was 6/6 in R. E. and 6/ in L. E. Plain skiagrams of skull and optic foramina were normal. V.D.R.L. was negative and other systems were also normal.

The ptos s in both eyes tended to increase after repeated excursions of the globe and increased markedly after voluntary closing and opening of the eyes in quick suc cessi n (*fig 4*) Patient was given a test dose of 1.5 mg of prostigmine by intramuscular njection, and after the injection pt s s in both eyes decreased considerably (*fig 5*) and the patient himself noticed that he could keep h s eyes open with ease. There was no change in other features

Comment

D ane s syndrome which has a varied aetiology is known to be associated with other ocular defects and with deformities in other parts of the body This is the



Fig 4
Appearance after lid exercise – increase in ptos s

The purpose of this paper is to report an interesting case of Duane's syndrome which was in association with myasthenia gravis

Case Report

G C aged 20 years male was admitted to the eye ward on 30 11 68 with the complaints of inability to open his eyes in sun sleepy eyes and narrowing of the space between the lids of his right eye for the last three months One and a half months later he noticed a similar narrowing in the left eye also and felt that he had to frown and make an effort to keep his eyes open There was no previous history of squint and the patient had no subjective symptom of diplopia

On examination he had mild bilateral ptosis noticeable more on the left side (fig 1) Movements of both eyes were full except for marked limitation of abduction of left eye (fig 3) There was retraction of the globe and narrowing of the palpebral fissure on adduction (fig 2) and widening of the fissure on abduction of the left eye (fig 3)



Fig 1
Patient looking straight ahead – bilateral ptosis

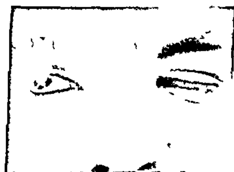


Fig 2
Adduction of left eye – retraction of globe and narrowing of palpebral fissure

7 *Gifford H* Congenital defects of abduction and other ocular movements and their relation to birth injury Amer J Ophth *9* 3 ?? 1926
8 *Pintucci & Ti io* J Genet Hum *10* 156 1961 cited in 5 p 993 995
9 *Pegenbogen L & R Stein* Crocodile tears associated with homolateral Duane s syndrome Ophthalmologica *156* 353 360 1968
10 *Sinclair W W* Abnormal associated movements of the eye lids Ophth Review *14* 307 319 1895
11 *Waardenburg* Klin Mbl Augenheilk *83* 774 1929 cited in 5 p 995
12 *Walsh F B* Clinical Neuro Ophthalmology Baltimore Williams and Wilkins Co 19 7 ed 2 p ?32
13 *Wildervanck* Ned T Geneesk *96* ?751 195? cited in 5 p 995



Fig 5
Appearance after injection of Prostigmine

first case of Duane s syndrome in combination with myasthenia gravis that the authors have seen It is difficult to decide whether the case is of preexisting Duane s syndrome in which myasthenia gravis appeared later – or one of recent myasthenia gravis with Duane s syndrome like manifestations But as Duane s syndrome is usually congenital it is more likely that the case is that of pre existing Duane s syndrome in which myasthenia gravis caused exaggeration of symptoms and led the patient to seek advice

Summary

An interesting case of Duane s retraction syndrome found in association with myasthenia gravis has been reported

References

1 *Aebli R* Retraction syndrome Arch Oph (Chicago) *10* 602 610 1933
2 *Bietti* Ann Ottal *32* 257 1903 cited in 5 p 993 995
3 *Danis* Ann Oculist (Paris) *181* 148 1948 cited in 5 p 993 995
4 *Duane A* Congenital deficiency of abduction associated with impairment of ab duction retraction movements contraction of palpebral fissure and oblique mo vements of the eye Arch Oph (Chicago) *34* 133 159 1905
5 *Duke Elder S* System of Ophthalmology *vol III* pt 2 London Henry Kimpton 1964 p 993 995
6 *Friedenwald H* Notes on congenital defects of the eye balls congenital paralysis of ocular muscles Bull John Hopkins Hosp 7 202 203 1896

all tissue up to the scleral junction except the peripheral pigment brim The corneas were immediately rinsed in sterile 0 9 % saline and put on a dish that was kept on ice in a thermos flask Most corneas were uncontaminated with blood those contaminated with blood after rinsing with saline were discarded The corneas were kept in the thermos flask until scraping off the epithelium which was performed within approximately two hours The scraping was per formed in as sterile conditions as possible with a Graefe s knife under a dis secting microscope The epithelium was then stored in small stoppered glass tubes at −26° C for up to three weeks before use Thawing was carried out at 4° C immediately prior to protein extraction Similar results were obtained by electrophoresis of proteins extracted from fresh corneas and from corneas stored for three weeks under the described conditions

Protein extraction

A By ultracentrifugation a perspex tube illustrated in Fig 1 was constructed for protein extraction At 4° C 40 μl of distilled water were applied in the bottom of the tube and 115 mg of bovine corneal epithelium were then placed above the water layer After ultracentrifugation at 36 000 rpm for 5 minutes at 4° C in a Spinco L50 preparative ultracentrifuge equipped with a SW39 head a water clear fluid was found above a layer of dense tissue material The fluid was carefully pipetted off mixed with a micro pipette and immediately there after subjected to electrophoresis The protein concentration was around 60



Fig 1
Schematic draw ng of perspex tube used for extraction of protein from bovine corneal epithel um by ultracentrifugation. Dimensions in mm

From Institute for Experimental Medical Research
Division of Immunology (Head Docent Morten Harboe M D)
University of Oslo Ullevål Hospital Oslo

AGAROSE GEL ELECTROPHORESIS OF PROTEINS FROM BOVINE CORNEAL EPITHELIUM

BY

BJØRN BERGER

The water soluble proteins of bovine corneal epithelium have previously been characterized by various forms of electrophoresis By paper electrophoresis the proteins have been separated into three to five fractions by various authors (cf *Miglior & Orzalesi* 1964) By high voltage electrophoresis in agar *François & Rabaey* (1963) found nine different fractions

The present experiments aimed at further characterization of water soluble proteins from bovine corneal epithelium by electrophoresis Agarose a purified polysaccharide component of agar was selected as supporting medium since this medium would also be suitable for further immunological studies of the separated proteins

By low voltage electrophoresis in agarose thirteen different protein bands and a more diffuse protein area were identified An additional band was observed which stained intensely with the periodic acid Schiff reaction and gave negative reactions with protein stains This fraction probably represents a carbohydrate

Material and Methods

Corneas The corneas were collected in the Oslo city slaughter house approximately 15 minutes after the death of the animal They were excised to include

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1 Electrophoresis was carried out at 4° C with a barbital buffer of pH 8 6 and ionic strength 0 05 in the gel while the concentration of agarose was varied and used as 2 % 1 % and 0 75 % 0 50 % agarose was too soft for preparation of the application groove The separation was similar in 1 % and 0 75 % agarose resulting in eleven protein bands With 2 % agarose there was considerable precipitation of protein in the gel close to the application groove which dried out rapidly during electrophoresis and only eight bands could be delineated Based on this experiment a concentration of 0 75 % agarose was used for electrophoresis

2 The concentration of buffer was varied so that the final ionic strength of barbital buffer of pH 8 6 in 0 75 % agarose was 0 06 0 03 0 02 and 0 015 At ionic strength 0 06 the electrophoretic separation was poor only nine bands could be delineated with weak and diffuse peripheral bands Protein precipitated in the gel close to the application groove which dried out rapidly during electrophoresis With barbital buffer of ionic strength 0 03 better separation was obtained Separation was optimal at ionic strength 0 02 and further reduction in ionic strength to 0 015 resulted in less satisfactory resolution with formation of diffuse bands A barbital buffer of ionic strength 0 02 was therefore selected for further experiments

3 Under these defined conditions electrophoresis was carried out at 4° C and 20° C The separation was superior at 4° C At 20° C 10 bands could be delineated and protein precipitated in the gel close to the application groove Based on this experiment a temperature of 4° C was used for electrophoresis

4 After optimal conditions had been worked out for electrophoresis in barbital buffer of pH 8 6 experiments were performed to separate the proteins under identical conditions with regard to agarose concentration temperature during electrophoresis and ionic strength of buffer in the gel now varying the pH Phosphate buffers of pH 5 8 and 7 4 were used At pH 5 8 protein precipitated in the application groove At pH 7 4 there were no protein precipitates in the application groove but fewer bands were found than with electrophoresis at pH 8 6 in barbital buffer Barbital buffer of pH 8 6 was therefore selected for the routine method

Fixation and further preparation of the gel Immediately after electrophoresis the gel was fixed for 3 hours in a solution of 5 % acetic acid in 90 % ethanol Gels to be stained with Sudan Black were either fixed in 2 % acetic acid for 3 hours or as described above After fixation the plates were dried overnight to a thin film under a moist filter paper at 45° C

Staining reactions Proteins were stained for four hours with a solution of Amido Black 10 B (Amidoschwarz 10 B Merck Darmstadt Germany) of the following composition 0 5 g Amido Black 10 B 450 ml 0 1 M sodium acetate 450 ml 0 1 M acetic acid and 100 ml glycerol Destaining was carried out for one hour in two subsequent baths of 2 % acetic acid

mg/ml in the extract The extracts were tested for bacterial contamination by cultures on blood agar no growth was observed after 24 hours

B By homogenization 1 25 ml of distilled water and 1100 mg of bovine epithelium were placed in a Sorval micro mixer and the capsule containing the tissue was covered with ice Homogenization was carried out at near maximal speed for three periods of 3 minutes with a stop of 30 seconds between each period to avoid excessive heating The homogenate was then cleared by ultracentrifugation in a Spinco L50 preparative ultracentrifuge at 10 000 rpm for 15 minutes at 4° C A white "crust" was present on the top of the watery layer This was discarded and the rest of the fluid was pipetted off at 4° C, mixed by repeated aspirations in a Pasteur pipette and immediately examined by electrophoresis at 4° C This fluid was opaque the protein concentration was about 60 mg per ml

Electrophoresis was carried out at 4° C in agarose gel containing 0 75 % agarose (Behringwerke Marburg/Lahn Germany) with veronal buffer of pH 8 6 and final ionic strength in the gel of 0 02 Ten ml of agarose were poured on each 8 2 × 8 2 cm glass plate and placed at 4° C in a moist chamber where the gel was usually kept for up to 2 hours before electrophoresis A rectangular groove measuring 9 × 0 8 mm was cut 2 cm from the cathodal side of the plate with a metal punch and the gel gently removed by suction During electrophoresis of protein extracted by ultracentrifugation the application groove usually remained full of fluid During similar electrophoresis of the extract prepared by homogenization the amount of fluid in the application groove increased and ultimately overflowed Thin filter papers covering 5 mm of the agarose gel connected the gel with the electrode vessels which contained veronal buffer of pH 8 6 and ionic strength 0 05 Electrophoresis was carried out for approximately 2½ hours with a tension of 35 volts across the 8 2 cm plate Bovine serum albumin (BSA 10 mg/ml in 0 9 % saline) was mixed with Evans blue and used as a marker to control the electrophoresis The marker fluid was applied in a circular hole with 2 mm diameter and centre 9 mm from the cathodal side of the plate This was to prevent protein from moving into the electrode vessels since it was found that a part of the complex of Evans blue and BSA had a markedly increased electrophoretic mobility Electrophoresis continued until the leading edge of the most prominent part of the marker had moved to a point 59 mm from the cathodal side of the plate Band No 1 of the bovine corneal epithelial proteins had then moved to a point 8 mm from the anodal side of the glass plate

Variation of conditions for electrophoresis

The experiments were made using fresh extracts prepared by ultracentrifugation and with buffer of ionic strength 0 05 in the electrode vessels

The position of glycogen (glycogen from oyster and rabbit liver Kock Light Laboratories Colnbrook England) after electrophoresis was identified by PAS staining performed as recommended by *Grabar* (1964)

Immunoelectrophoresis The electrophoresis was carried out in the usual way but merthiolate dissolved in saline was added to the gel in a final concentration of 1 10 000 The antibody trough was 1 5 mm wide and placed 3 mm from the end of the application groove The plates were left at room temperature for 48 hours prior to reading and photography which was performed using a dark field illumination and unstained slides

Protein concentrations were determined by a modified Folin technique (*Lowry et al* 1951) The standard curve was drawn after determination of the Folin extinction value at 735 mμ of dilutions of a solution of bovine corneal epithelial proteins and simultaneous determination of the nitrogen content by the micro Kjeldal technique assuming the protein concentration to be 6 25 times the nitrogen value

Results

1) Electrophoresis

a Electrophoresis in agarose gel separated the proteins extracted from bovine corneal epithelium by ultracentrifugation into 13 bands and there was a marked background staining for protein from band No 5 to band No 13 (Fig 2) Fig 3 shows the density curve of this plate with the 13 components numbered

Band No 1 was strongly stained with Sudan Black B Band No 2 was faintly stained with Sudan Black B whereas the remaining bands showed no staining for lipid These results were obtained both after fixation of the gel in 2% acetic acid and in 5% acetic acid in 90% ethanol

By immunoelectrophoresis of proteins extracted from bovine corneal epithelium against anti bovine serum bovine serum albumin was identified in an area corresponding to the broad band No 5 Band No 5 or a part of it is thus due to albumin

PAS staining after electrophoresis of the extract of bovine corneal epithelium revealed one intensely stained band with a mobility that did not correspond to any protein fraction (Fig 4) Glycogen showed similar mobility in comparative experiments

The relative distribution of the various protein fractions was determined by scanning after electrophoresis (Fig 3) The distribution is given in Table I

Table II shows the relative electrophoretic mobilities of the most distinct protein fractions Fractions 12 and 13 are the only fractions with negative electrophoretic mobility The Mr values shown in Table II were calculated

The periodic acid Schiff (PAS) staining reaction was performed according to *Grabar* (1964) using the optional procedure with treatment of the plates for 15 minutes with hydroxylamin HCl In reference electrophoretic experiments dextran was stained by the PAS reaction with the following modifications to Grabar s procedure the hydroxylamin HCl bath was not used staining with Schiff s reagent was prolonged to 30 minutes, and the washings in sulphurous acid were omitted

Staining with Sudan Black B was performed as recommended by *Grabar* (1964) with a saturated solution of Sudan Black B in 60 % ethanol for 16 hours followed by destaining for 15 minutes in two subsequent baths with 50 % ethanol

To ascertain that there was no contamination with blood in the protein extract the benzidine peroxidase reaction was carried out immediately after stopping electrophoresis by exposing the gel to a freshly prepared benzidine solution in acetic acid with H_2O The reaction was negative

Scanning Scanning was performed in a Joyce Chromoscan with an optical slit of 0 5 mm with blue filter 50 22 The length of the measuring slit was slightly less than the zones scanned The apparatus provided automatic transport of the electrophoretic slide coupled with recording and integration to determine the percentage distribution of the various fractions

Reference electrophoresis and calculation of relative electrophoretic mobilities (Mr values) A reference solution containing human serum albumin human transferrin and dextran all at a concentration of 10 mg/ml in barbital buffer was used for determination of relative electrophoretic mobility The reference mixture was run in parallel with a solution of bovine corneal epithelial proteins on the same plate In Fig 2 the position of dextran was marked with a grease pencil below the glass plate prior to photography This was possible since the peripheral borders of the dextran are easily visible without PAS staining after drying the plates The Mr values of the different protein fractions were calculated according to Wieme s formula (1965) using human serum albumin (Mr = 1) and dextran (Mr = 0) as reference substances To obtain maximal accuracy in calculating the Mr values the plates were scanned and the localization of the various protein fractions determined according to maximal optical density The distance in mm from this point to the middle line of the application groove was determined with subsequent calculation of the Mr values In some experiments Mr values were calculated after measurements on a photograph enlarged 2 5 times from the original electrophoretic plate Similar results were obtained with the two methods Wieme recommends the use of transferrin as a control substance for electrophoresis and calculation According to Wieme a transferrin Mr value of 0 49 should be obtained in 1 % agar gel with barbital buffer of pH 8 4 of ionic strength 0 05 The Mr value of transferrin in the present system was 0 49

The position of glycogen (glycogen from oyster and rabbit liver Kock Light Laboratories Colnbrook England) after electrophoresis was identified by PAS staining performed as recommended by *Grabar* (1964)

Immunoelectrophoresis The electrophoresis was carried out in the usual way but merthiolate dissolved in saline was added to the gel in a final concentration of 1 10 000 The antibody trough was 1 5 mm wide and placed 3 mm from the end of the application groove The plates were left at room temperature for 48 hours prior to reading and photography which was performed using a dark field illumination and unstained slides

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Fig 2

Electrophoresis of protein extracted from bovine corneal epithelium by ultracentrifugation Appearance of the original electrophoresis (top) Reference electrophoresis of a mixture containing human serum albumin transferrin and dextran (centre) The position of dextran is marked with a grease pencil below the glass plate Schematic drawing of electrophoresis (bottom) The bands were sharply demarcated except bands Nos 5 6 7 and 9 Between bands Nos 5 and 13 there is a continuous area staining for protein as indicated Occasionally two diffuse bands appeared between bands Nos 8 and 10 Arrow marks application groove Anode to the left

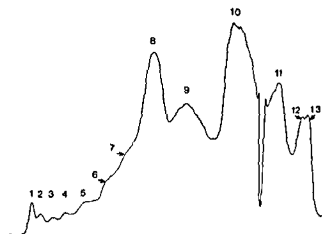


Fig 3

Density curve after scanning of electrophoretic plate shown in Fig 2

from the plate illustrated in Figs 2 and 3 In addition Mr values were calculated from three further plates by the photographic method The mean Mr values calculated in this way agreed closely with the values given in Table II The maximal deviation of a single Mr value from the values of Table II was 0 03

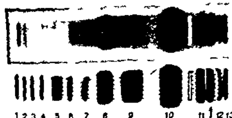


Fig 4

Electrophoresis of proteins extracted from bovine corneal epithelium by ultracentrifugation The slide was first stained with periodic acid Schiff reagent and later with Amido Black B In addition to the 13 protein bands also shown in Fig 2 one band stained intensely with PAS stain (arrow) This band is situated close to band No 11 so that the peripheral borders of these bands approach each other

Table I

Relative distribution of protein fractions after electrophoresis of an aqueous extract of bovine corneal epithelium prepared by ultracentrifugation

Fraction	Relative concentration %
1 5	9 2
6 and 7	6 8
8	10
protein between fractions 8 and 10	19 6
10	25 4
11	15 5
12	5 8
13	3 3

b Electrophoresis of proteins extracted by homogenization of corneal epithelium Electrophoresis in agarose gel provided 13 bands Again there was a continuous area which stained markedly for protein from band 5 to band 13 (Fig 5) The main difference between this pattern and electrophoresis of proteins extracted by ultracentrifugation is the marked precipitation of protein at the anodic side of the application groove and the striated lines between bands 9 and 10 The density curve after electrophoresis of proteins extracted by this technique is shown in Fig 6

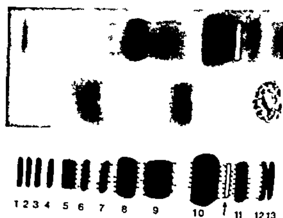


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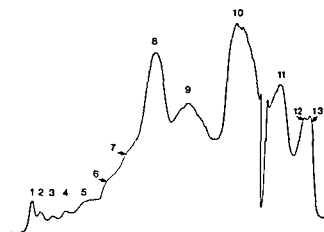


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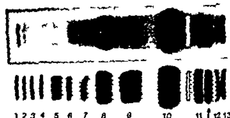


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Electrophoresis of proteins extracted from bovine corneal epithelium by ultracentrifugation. The slide was first stained with periodic acid Schiff reagent and later with Amido Black B. In addition to the 13 protein bands also shown in Fig 2 one band stained intensely with PAS stain (arrow). This band is situated close to band No 11 so that the peripheral borders of these bands approach each other

Table I

Relative distribution of protein fractions after electrophoresis of an aqueous extract of bovine corneal epithelium prepared by ultracentrifugation

Fraction	Relative concentration %
1–5	2.0
6 and 7	6.8
8	19
protein between fractions 8 and 10	19.6
10	28.4
11	13.5
12	5.8
13	3.3

b Electrophoresis of proteins extracted by homogenization of corneal epithelium. Electrophoresis in agarose gel provided 13 bands. Again there was a continuous area which stained markedly for protein from band 5 to band 13 (Fig 5). The main difference between this pattern and electrophoresis of proteins extracted by ultracentrifugation is the marked precipitation of protein at the anodic side of the application groove and the striated lines between bands 9 and 10. The density curve after electrophoresis of proteins extracted by this technique is shown in Fig 6

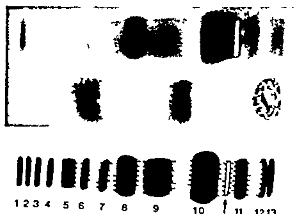


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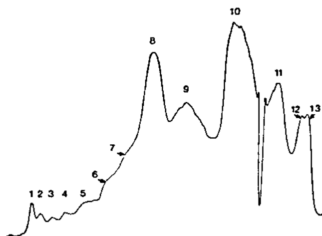


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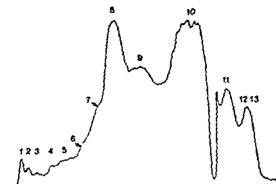


Fig 6

Density curve after scanning of the electrophoretic plate shown in Fig 5

trophoresis using a potent antiserum produced against bovine serum After immunoelectrophoresis in agarose of an extract prepared by ultracentrifugation containing 60 mg protein per ml several precipitin lines appeared (Fig 7A) Only precipitates Nos 1 and 2 were considered to be due to specific immune reactions between serum proteins in the extract and the antiserum used The other precipitates were also observed when the antiserum was exchanged with a normal rabbit serum which did not precipitate with bovine serum proteins cf Fig 7B

The position of precipitate No 1 corresponded to the position of bovine serum albumin An identical precipitin line developed with the use of specific

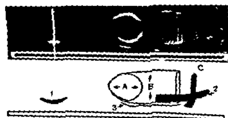


Fig 7A

Photograph and drawing of immunoelectrophoresis in agarose of proteins from bovine corneal epithelium extracted by ultracentrifugation The extract was tested in a concentration of 60 mg per ml against a potent anti bovine serum For identification of the various precipitates see text The vertical line near the anodic end of the plate is scratched under the glass plate to show the position of the marker containing bovine serum albumin labelled with Evans Blue

Table II

Relative electrophoretic mobility of the most distinct protein fractions in an aqueous extract of bovine corneal epithelium

Fraction 1	Mr = 1 38
Fraction 2	Mr = 1 34
Fraction 3	Mr = 1 29
Fraction 4	Mr = 1 21
Fraction 8	Mr = 0 77
Fraction 10	Mr = 0 34
Fraction 11	Mr = 0 09
Fraction 12	Mr = - 0 04
Fraction 13	Mr = - 0 07
Reference substances	
Human serum albumin	Mr = 1 00
Dextran	Mr = 0 00
Human transferrin observed	Mr = 0 49

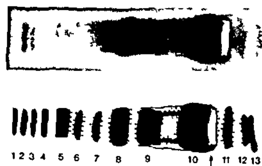


Fig 5

Photograph and schematic drawing of electrophoresis of proteins extracted from bovine corneal epithelium by homogenization Protein concentration of extract 60 mg per ml The bands are sharply demarcated except bands Nos 5 6 and 7 and particularly band No 9 which has very diffuse borders Between bands Nos 5 and 13 there is a continuous area stained for protein as indicated on the drawing There are some striated lines between fractions 9 and 10 (see drawing) Considerable precipitation of protein is seen on the anodic side of the application groove which is deformed on the anodic side

2) Immunoelectrophoresis

To ascertain whether some of the protein extracted from bovine corneal epithelium represented bovine serum proteins the extract was tested by immunoelec

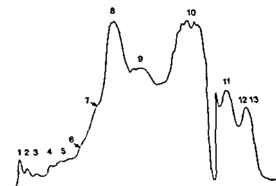


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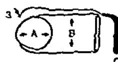


Fig 7B
Photograph and drawing of immunoelectrophoresis performed under identical conditions as in *Fig 7A* except that a normal rabbit serum was used in the antibody trough.



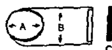


Fig 7C
Photograph and drawing after electrophoresis of the same extract in agarose. The gel was left at room temperature for 48 hours and then photographed There was no rabbit serum in the trough

anti BSA Repeated immunoelectrophoreses showed that the point of precipitate 1 closest to the antibody trough corresponded to the position of band No 5 This finding indicates that band No 5 or protein making up a part of this band is bovine serum albumin

Precipitate No 2 of Fig 7A is very weak Its position corresponds to the area of serum γG globulin and was therefore considered to be due to trace amounts of serum G globulin present in the extract of bovine corneal epithelium

The other lines denoted 3 A and B which were very similar to precipitin lines and the band formed precipitate marked C were also observed when the epithelial extract was tested in immunoelectrophoresis against normal rabbit serum (Fig 7B)

The precipitates marked A and B in Figs 7A and 7B and the band denoted C were also observed when an agarose gel was left at room temperature for 48

hours after electrophoresis without adding rabbit serum (Fig 7C) They are evidently due to spontaneous precipitation in the gel

Discussion

Proteins were extracted from bovine corneal epithelium by direct ultracentrifugation of the tissue in a perspex tube fitted to the SW 39 rotor and by homogenization of the tissue in distilled water followed by centrifugation The two extracts had quite different properties fresh extracts prepared by ultracentrifugation were water clear whereas samples made by homogenization were opaque During electrophoresis the two types of extracts behaved differently (Figs 2 and 5) The application groove regularly widened during electrophoresis of extract obtained by homogenization and protein precipitated heavily in the agarose gel immediately anodically of the application groove Additional striated lines are also seen between bands 9 and 10 of Fig 5 when compared with Fig 2 which shows electrophoresis of proteins extracted by ultracentrifugation The opacity of the fresh extract prepared by homogenization and these changes in the gel are probably due to aggregation of some of the soluble proteins When a sample containing such aggregates is put into the application groove and electrophoresis started the aggregated proteins will move towards the anode The largest aggregates will not enter the gel but will be stuck to the side of the groove with subsequent deformation The somewhat smaller aggregates will penetrate the gel and form striated lines

The ultracentrifugation procedure probably works by compressing the cells which results in extrusion of inter and intracellular fluid which then mixes with the distilled water present in the tube This extraction procedure appeared to be very gentle and resulted in a minimum of aggregate formation when carried out at 4° C Homogenization of the corneal epithelium induced aggregation of some of the proteins and the fluid remained opaque after ultracentrifugation at 36 000 rpm for five minutes Comparison of Figs 2 and 5 and the corresponding density curves (Figs 3 and 6) shows that none of the main protein fractions was absent in the extract prepared by ultracentrifugation the yield of protein thus appears to be satisfactory The extraction by ultracentrifugation had one further advantage it may easily be used as a micro method which provides a fresh extract with high protein concentration when only small amounts of tissue are available for extraction

A series of experiments described under Variation of conditions for electrophoresis showed that the best electrophoretic separation in agarose of water soluble proteins from bovine corneal epithelium was obtained by the use of a gel containing 0 75 % agarose and ionic strength of 0 02 in the barbital buffer



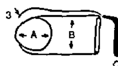


Fig 7B
Photograph and drawing of immunoelectrophoresis performed under identical conditions as in Fig 7A except that a normal rabbit serum was used in the antibody trough



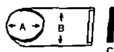


Fig 7C
Photograph and drawing after electrophoresis of the same extract in agarose The gel was left at room temperature for 48 hours and then photographed There was no rabbit serum in the trough

anti BSA Repeated immunoelectrophoreses showed that the point of precipitate 1 closest to the antibody trough corresponded to the position of band No 5 This finding indicates that band No 5 or protein making up a part of this band is bovine serum albumin

Precipitate No 2 of Fig 7A is very weak Its position corresponds to the area of serum γG globulin and was therefore considered to be due to trace amounts of serum γG globulin present in the extract of bovine corneal epithelium

The other lines denoted 3 A and B which were very similar to precipitin lines and the band formed precipitate marked C were also observed when the epithelial extract was tested in immunoelectrophoresis against normal rabbit serum (Fig 7B)

The precipitates marked A and B in Figs 7A and 7B and the band denoted C were also observed when an agarose gel was left at room temperature for 48

ner as with natural human antibodies against lens proteins (*Hackett & Thompson* 1964)

Agarose was selected as supporting medium for electrophoresis since it is also useful for additional immunological studies of the individual protein fractions The results of these studies will be reported in separate papers

Summary

By agarose gel electrophoresis of water soluble proteins extracted from bovine corneal epithelium 13 protein bands were found in addition to a large continuous protein area which was distributed from band No 5 to band No 13 One band was intensely stained by the periodic acid Schiff (PAS) reagent but did not stain with Amido Black or Sudan Black and probably represents a carbohydrate

The protein patterns were critically dependent on conditions during electrophoresis and on the method of protein extraction A micro technique for extraction of proteins from bovine corneal epithelium by ultracentrifugation is described the technique is gentle and a water clear solution of high protein concentration is obtained With extraction following homogenization proteins showed a marked tendency to aggregate

Acknowledgement

The author is indebted to Docent M Harboe for valuable discussions

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of pH 8 6 with electrophoresis being carried out at 4° C These conditions were therefore used in all subsequent experiments

Fig 2 shows that electrophoresis in agarose gel separated the proteins extracted from bovine corneal epithelium into 13 bands in addition there was a continuous area which stained markedly for protein from band No 5 to band No 13 with maximal intensity between bands Nos 8 and 10 Several earlier authors have used paper electrophoresis to characterize proteins from bovine corneal epithelium The proteins were separated into three to five fractions (cf *Miglior & Orzalesi 1964*) *François & Rabaey (1963)* used high voltage electrophoresis in agar gel and their density curves showed up to nine different fractions Their "principal fraction" probably corresponds to the electrophoretic fraction denoted 10 in the present paper This is the largest of the electrophoretic fractions amounting to 28 4 % of the total protein

After electrophoresis one band stained intensely with PAS this band was not stained with Amido Black nor with Sudan Black These properties indicate that this band is due to a carbohydrate It may be due to glycogen which is present in bovine corneal epithelium constituting 7 5 % of its dry weight (*Hermann & Hickman* 1928) it was found that glycogen has an electrophoretic mobility similar to the PAS positive band

The PAS positive fraction seems to have the same position as the PAS positive fraction described by *François et al* (1961) These authors considered this fraction to be due to a glycoprotein but their view could not be confirmed in the present experiments since the fraction staining with PAS did not stain with Amido Black

Protein bands Nos 1 and 2 also stained with Sudan Black B indicating that they are lipoproteins

By immunoelectrophoresis serum albumin and a trace of γG globulin were demonstrated in the extract Albumin corresponded in position to band 5 indicating that this band or part of it is due to albumin Serum albumin has previously been demonstrated in extracts of bovine corneal epithelium by *Kaucran & Ott* (1961) The γG globulin gave a diffuse smear on both sides of the application groove it was present in low concentration and thus cannot contribute significantly to any of the electrophoretic bands in this area

After immunoelectrophoresis of extracts of bovine corneal epithelium with normal rabbit serum in the trough precipitates were also observed Precipitates were again seen after electrophoresis of extracts of bovine corneal epithelium when the gel was incubated at room temperature for 48 hours (Fig 7C) Although two of these precipitates are very similar to immune precipitates they should not be confused Precipitate No 3 (Fig 7B), however must be due to some interaction between normal rabbit serum and protein in the extract The nature of this interaction is unknown it may be due to a natural antibody against a constituent in corneal epithelium which reacts across the species bar

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Department of Ophthalmology Irwin Hospital
New Delhi India

BILATERAL PERIPHERAL SCLERO CORNEA

BY

D K. SEN M S HARI MOHAN F R C S and
D K. GUPTA M S

This is a condition of opacification of the peripheral parts of the cornea so that this tissue appears to blend with the sclera making the limbus unrecognisable Such scleralization of the cornea is rare and is usually met with in cases of cornea plana The condition is often associated with other local and systemic anomalies like microphthalmos anomalies at the angle of the anterior chamber (*Franceschetti* 1946 *Goldstein & Cogan* 1962 *Malik et al* 1965) polydactyly lacunae of the parietal bones cranial dystrophies deformities of the ear and congenital cerebellar symptoms (*Goldstein & Cogan* 1962)

This case is reported because none of these abnormalities were present and the condition occurred as an isolated congenital anomaly which is considered very rare

Case report

M 45 years old Muslim male attended the eye outpatient department of Irwin Hospital with the complaints of defective vision in both the eyes for several years

On examination

Vision in both the eyes was 6/18 which was correctable to 6/9 + with convex lenses Findings were similar and symmetrical on both the sides (Fig I) The dimensions and the curvature of cornea were n rmal So also the dimensions of the globe The peri

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Fig 3

16 20 mm stage when the cornea is developing as suggested by *Duke Elder* (1964) As the patient was not visually handicapped because of this he was least concerned about the anomaly

Peripheral sclero cornea may sometimes be misdiagnosed and treated as vascular keratitis but absence of any sign or symptom of inflammation should *help to diagnose the condition differentially*

Summary

A case of bilateral peripheral sclero cornea is reported because of the rarity of the condition and also because it was present in an eye which was otherwise normal and was not associated with any other local or systemic congenital ab normality

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Fig 1

pheral portion of the cornea was white and indistinguishable from the sclera Sclera lization was more marked above and below thereby causing the clear portion of the cornea to look horizontally oval (6 5 mm × 5 mm) (Fig II and III) Fine arcades of superficial scleral vessels invaded the cornea all around the periphery in a regular fashion There was no evidence of any inflammation The eyes were normal in all other respects

On enquiring it was found out that the anomaly had been with him since birth and it had not progressed Family history was negative

Comments

Scleralization of the cornea occurred in this case as a primary anomaly probably due to an aberration of the paraxial mesoderm anterior to the optic cup at the



Fig 2

Ocular findings

The right eye showed a swelling (1.5 cm × 1 0 cm) partly invading the lower and outer part of cornea and extending towards the inferior fornix (Figure 1) The part of this mass over the cornea was white firm and well defined while the part of the swel lin over the conjunctiva was reddish soft and ill defined Ocular movements were perfectly normal The anterior chamber iris and lens and ocular fundus showed no abnormality

Other associated abnormalities

Face showed marked asymmetry Right cheek and right mandibular region was flat as compared to the other side (Figure 2) The right masseter and temporalis muscles



Fig 1



Fig 2

Department of Ophthalmology Irwin Hospital
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THE SYNDROME OF GOLDENHAR

(Oculo-Auricular Dysplasia)

BY

D K SEN M S HARI MOHAN F R C S and
D K GUPTA M S

The syndrome of Goldenhar is characterized by a triad of anomalies comprising epibulbar dermoids accessory auricular appendages and aural fistulae The condition is unilateral occurs only sporadically and is sometimes associated with other ocular anomalies like coloboma of the upper lid microphthalmos and ocular colobomata More rarely other facial and widespread nervous muscular and skeletal anomalies may be in association with the ocular dermoids and aural deformities (*Duke-Elder* 1964)

Though external aural deformities are a part of this syndrome middle ear anomalies giving rise to congenital deafness must be very rare We have not come across any reference to this in the literature available to us Moreover the association of congenital deafness and facial hemiatrophy has an interesting embryological explanation worth recording

Case report

A K 5 years old Hindu male child reported to the Ophthalmic O P D of Irwin Hospital New Delhi with the complaints of a swelling in the inferotemporal part of the right eye present since birth and which had been gradually increasing since then Vision was not affected

Received February 18th 1969

Ocular findings

The right eye showed a swelling (1.5 cm × 1.0 cm) partly invading the lower and outer part of cornea and extending towards the inferior fornix (Figure 1). The part of this mass over the cornea was white, firm and well defined, while the part of the swelling over the conjunctiva was reddish, soft and ill defined. Ocular movements were perfectly normal. The anterior chamber, iris and lens and ocular fundus showed no abnormality.

Other associated abnormalities

Face showed marked asymmetry. Right cheek and right mandibular region was flat as compared to the other side (Figure 2). The right masseter and temporalis muscles



Fig 1



Fig 2

were not palpable even on clinching the teeth suggesting its absence or hypoplasia Skiagrams showed hypoplasia of the right maxilla and right mandible

Two auricular appendages were present about 3 cms infront of the right tragus (Figure 3)

ENT examination did not reveal any abnormality excepting the presence of the auricular tags which are shown in the photograph Routine audiogram revealed right sided conductive deafness suggesting the association of middle ear anomaly Hearing on the left side was normal

Audiogram results

Right side

	125	250	500	1000	2000	4000	8000	cps
AC	55	50	40	45	40	40	30	dB
BC			5	0	0	5		dB
Left side								
AC	10	5	10	10	5	10	10	dB
BC			5	0	5	5		dB

Parents of the child were asked to give consent for exploratory tympanotomy and correction of the middle ear anomaly if possible but they did not agree However they agree for removal of the limbal dermoid under general anaesthesia (Figure 4) Histopathological examination of the tumour removed confirmed it to be a dermoid

Discussion and Comments

The etiology of the epibulbar dermoids is disputed and may vary in different cases Classically dermoids are considered to be sequestrations of dermal tis

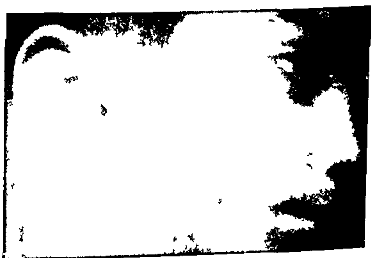


Fig 3



Fig 4

sues in the underlying layers However several authors have suggested that certain epibulbar dermoids may represent the residue of amniotic adhesions Such an explanation might account for some cases but keeping in view the other associated anomalies we are more inclined to consider genetic abnormality as the cause in this case

It is a fact that second arch artery takes over the task of supplying nutrition to the first arch elements besides its own area of supply during the critical period between the disappearance of the first arch artery and the appearance of the external carotid artery *(Fernande & Ponis* 1964) Any deleterious influence therefore at this period jeopardising the function of the second arch artery would affect the elements of both the first arch and second arch This would explain the association of congenital facial hemiatrophy with aural anomalies including conductive deafness as pinna develops from the first and the second arch elements and so also do the ossicles (malleus and incus from the first arch and stapes from the second) Pre auricular fistula was not present in this case presumably because apart from possible appearance of the ectopic auricular appendages the fusion between the knobs of His was not faulty

As mentioned before since no attributable factor could be elicited it is presumed that the anomalies were of genetic origin However it is possible that the multiple anomalies of the different embryologically unrelated structures have resulted from some noxious element playing an injurious role at the same stage of development

So the case may be considered as an atypical case of Goldenhar s syndrome

Summary

A case of atypical Goldenhar s syndrome with congenital conductive deafness and facial hemiatrophy is presented An attempt has been made to give em

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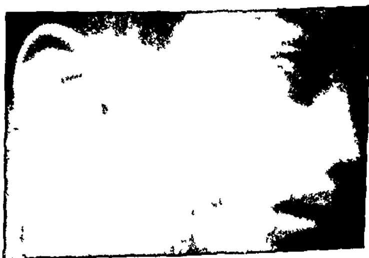


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Summary

A case of atypical Goldenhar s syndrome with congenital conductive deafness and facial hemiatrophy is presented An attempt has been made to give em

bryological explanation for the various anomalies that are in association with ocular dermoid

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Fernandez A O & M L Ronis AMA Arch otolaryng *80 505*

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Sabbatsberg Hospital Stockholm Sweden

GLAUCOMA MIOTIC THERAPY AND CATARACT

V Studies on the lens in glaucoma eyes after discontinuance of echothiophate (Phospholine Iodide) therapy

BY

UNO AXELSSON

Introduction

Previous studies have shown that echothiophate (Phospholine Iodide) may produce cataract (*Axelsson & Holmberg* 1966 *Axelsson* 1968 a b) This observation decided us to discontinue Phospholine Iodide therapy in all cases where this was possible Many patients who had been on the drug for at least six months were followed up with reference to the condition of the lens for more than two years after withdrawal In Part A of this paper the findings are reported on

A previous paper (*Axelsson* 1968 b) dealt with an investigation of the visual loss associated with lenticular changes occurring during Phospholine Iodide therapy in 126 patients (198 eyes) with chronic simple glaucoma who had been on the drug for at least six months Since in many cases despite withdrawal of the drug vision continued to deteriorate owing to lenticular changes it was not possible to assess the effect of Phospholine Iodide therapy on the lens by the condition of the eyes determined at withdrawal of the drug Part B of this paper summarizes the findings in this series when many of the patients had been followed up for another three years

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bryological explanation for the various anomalies that are in association with ocular dermoid

References

Duke Elder S (1964) System of Ophthalmology Vol *3* Pt. II p 822 Henry Kimpton, London.

Fernandez A O & M L Ronis AMA Arch otolaryng *80* 505

Our aim was to assess the changes in the condition of the lens occurring during the follow up period on the basis of the concomitant changes in visual acuity This procedure could be confidently applied to the group of 104 eyes discussed since it included only three eyes with severe visual loss due to causes other than cataract vi amblyopia ex anopsia (two eyes) and macular degeneration (one eye) However it could reasonably be assumed that the visual acuity of some of the eyes classified as changed during Phospholine Iodide therapy would be reduced to a lesser degree after withdrawal of the drug owing to increased pupillary size Consequently the visual acuity determined on withdrawal of Phospholine Iodide could not be used as the initial visual acuity The findings at the end of the first and the second follow up years were therefore correlated with those of the first follow up examination after discontinuance of the treatment This examination was usually made within less than two months after discontinuance The following definitions are used *Impaired* eyes whose visual acuity had deteriorated by 2/10 or more due to lenticular changes *improved* eyes whose visual acuity had improved by 2/10 or more owing to changes in the condition of the lens *unchanged* eyes which did not fulfil any of the above mentioned criteria

For the eyes which were followed up for two years after discontinuance of Phospholine Iodide therapy the findings during each of these years are reported separately (see Table I)

Results and Comments

The results are given in Table I As it was considered of interest to investigate (i) whether the type of cataract characterized by ASCV progressed after Phospholine Iodide withdrawal and (ii) whether there was a difference with regard to the progression of cataract between the eyes classified respectively as changed and unchanged during Phospholine Iodide therapy the group of eyes investigated was subdivided as shown in the table The following comments can be made

1 In the two subgroups of eyes without ASCV which comprised 39 eyes only insignificant changes were observed All eyes classified as unchanged during Phospholine Iodide therapy remained *uncharged also* during this follow up Out of seven eyes classified as changed during Phospholine Iodide therapy six were unchanged one year and five unchanged two years after withdrawal of the drug In none of these 39 ev s were *ASCV developed* during the follow up period

2 In the two subgroups consisting of 65 eyes with ASCV more pronounced changes were observed Out of 33 eyes classified as unchanged during Phospho

Part A

Material and Methods

In the above mentioned series consisting of 198 eyes Phospholine Iodide was either withdrawn or replaced by weak miotics (pilocarpine or pilocarpine eserine) in 112 eyes with their lenses sufficiently intact to permit the assessment of any further lenticular changes Our aim was to investigate the condition of these eyes one and two years after the withdrawal of the drug

Two patients (three eyes) failed to attend during the first year of the follow up On another five eyes cataract extraction was performed owing to progression of the lenticular changes Thus there were 104 eyes available for reexamination and assessment of changes in the condition of the lens one year after Phospholine Iodide withdrawal Out of these 104 eyes 47 had been treated with 0 06 % Phospholine Iodide solutions and 43 with 0 25 % solutions In 14 eyes the initial dose had been 0 06 % Phospholine Iodide and at a later stage 0 125 % (two eyes) or 0 25 % of the drug had been instilled Following withdrawal eight eyes were normotensive and remained so without treatment in the other 96 eyes tension was adequately controlled with weak miotics which were combined with epinephrine derivates and/or carbonic anhydrase inhibitors in 52 of these eyes

During the second year of the follow up three more patients (five eyes) failed to attend On eight eyes cataract extraction was performed In seven other eyes the cataractous involvement was so extensive already in the first follow up year that assessment of any further lenticular changes would have been difficult consequently these eyes were excluded Hence there were 84 eyes available for examination and evaluation of lenticular changes two years after Phospholine Iodide withdrawal

All patients were regularly followed up at the clinic usually at intervals of three months The follow up examinations one and two years after Phospholine Iodide withdrawal were all made by the author For details of the methods of examination see *Axelsson* 1968a b

It was found that typical anterior subcapsular vacuoles (ASCV) are characteristic of cataract induced by Phospholine Iodide (*Axelsson & Holmberg* 1966 *Axelsson* 1968a) Of the 104 eyes available for follow up examination one year after discontinuing Phospholine Iodide therapy 98 eyes had previously been examined with special reference to the presence of ASCV at or within four months of Phospholine Iodide withdrawal and the other six eyes about six months after withdrawal According to the findings on these occasions the eyes were classified either as *eyes with ASCV* or *eyes without ASCV* The eyes in which during Phospholine Iodide treatment the visual acuity deteriorated by 2/10 or more due to lenticular changes are referred to as *eyes changed during Phospholine Iodide therapy* All other eyes are referred to as *eyes unchanged during Phospholine Iodide therapy*

line Iodide therapy the lenticular changes progressed during the first follow up year in 9(28 %) The corresponding figure for 32 eyes classified as changed during Phospholine Iodide therapy was 20(61 %) On the other hand the condition of the lenses in two eyes improved in the latter group

The lenses of 18 eyes in these subgroups could not be reexamined two years after Phospholine Iodide withdrawal mainly because cataract extraction had been performed or dense or almost dense cataracts had developed during the first follow up year Analysis of the eyes reexamined two years after withdrawal of the drug shows that many eyes which had been impaired during the first follow up year did not continue to deteriorate during the second It is interesting to note that the condition of five eyes which had been impaired or had remained unchanged during the first follow up year improved during the second

The above observations show that the type of cataract characterized by ASCV progressed in many eyes in this series after Phospholine Iodide withdrawal especially during the first year after this Obviously there is great danger of the cataract progressing if the drug is withdrawn when vision is already affected But there is also danger of cataract progression if Phospholine Iodide therapy is discontinued at an earlier stage *i e* before vision has been affected

3 Thus the behaviour of the eyes with ASCV varied after Phospholine Iodide withdrawal Consequently from the observations made in this investigation no definite conclusions can be drawn concerning the behaviour of a damaged lens after the discontinuance of Phospholine Iodide therapy However some usual course of events were observed

If at the time Phospholine Iodide therapy was discontinued the cataractous changes involved the deeper layers of the lens they usually progressed and caused total or subtotal cataracts especially in elderly patients

If when Phospholine Iodide was withdrawn the principal lenticular lesion consisted of ASCV then the course was different During the first three or four months after withdrawal the ASCV often progressed In some eyes this seemed to initiate a rapid clouding of the lens In many eyes however a layer of apparently healthy lens fibers gradually appeared under the capsule and displaced the affected fibers deeper into the lens Concurrently the ASCV underwent changes which occasionally resulted in improved vision Coalescence of vacuoles to form large vacuoles was frequently seen In some cases particularly in the presence of extensive vacuolation the vacuoles were observed to be clustered together forming sharply demarcated plaques surrounded by zones of clear lenticular substance Especially in young patients and in less extensive vacuolation the vacuoles often seemed compressed forming sharply outlined dots arranged in clusters or dendriform chains In some cases the vacuoles became so small that they might easily have been overlooked if their presence

Table I

Findings in 104 and 84 eyes with chronic simple glaucoma treated with Phospholine Iodide for at least six months and followed up with regard to changes in condition of the lens respectively one and two years after withdrawal of the drug The group of eyes investigated is subdivided according to presence or absence of ASCV and to unchanged or changed (see definition in text) during Phospholine Iodide therapy

Symbols \— = impaired first year unchanged second year —/ = unchanged first year improved second year etc

Subgroup		Evaluation one year after withdrawal of Phospholine Iodide				Evaluation two years after withdrawal of Phospholine Iodide										
							Improved			Unchanged			Impaired			
ASCV	Changed during Phospholine Iodide therapy	Total No eyes	Improved No eyes	Unchanged No eyes	Impaired No eyes	Total No eyes	—/ No eyes	// No eyes	/— No eyes	—— No eyes	\/ No eyes	/\ No eyes	\— No eyes	—\ No eyes	\\ No eyes
No	No	32	–	32	0	31	–	–	–	31	0	0	0	0	0
No	Yes	7	0	6	1	6	0	0	0	5	0	0	0	0	1
Yes	No	32	–	23	9	29	–	–	–	21	1	0	4	2	1
Yes	Yes	33	2	11	20	18	2	1	1	5	2	0	4	0	3

126 patients (198 eyes) with chronic simple glaucoma treated with Phospholine Iodide in various concentrations for at least six months The series is described in detail in previous papers (*Axelsson* 1968a b) These patients have been observed at the clinic for periods ranging from six months to eight years after Phospholine Iodide therapy was begun Out of the 198 eyes 59 had been treated with the drug for less than 12 months and 61 other eyes for less than 18 months Only in 27 eyes had the drug been administered for more than three years

The assessment is based on the findings at the last examination of the patients in the clinic In some cases Phospholine Iodide was withdrawn either because it had to be replaced by some other long acting cholinesterase inhibitor or because glaucoma surgery had to be performed For these cases assessment is based on the findings at the time of Phospholine Iodide withdrawal

Results and Comments

The following comments can be made on the results which are given in Table II

Out of the 108 eyes whose visual acuity had deteriorated by 2/10 or more owing to development or progression of cataracts 77 had clear lenses or only minimal cataractous changes when Phospholine Iodide therapy was begun their visual acuities were 0 7 or more at the first examination after the drug was administered Only 8 eyes had an initial visual acuity of 0 3 or less which

Table II

Findings in 126 patients (198 eyes) with chronic simple glaucoma treated with Phospholine Iodide for at least six months and observed for from six months up to eight years

	No eyes	% of total
Visual acuity deteriorated by 2/10 or more owing to development or progression of cataracts	108	54
Cataractous changes characterized by ASCV observed but either no deterioration of visual acuity or less than 2/10	30	15
Change in the condition of the lens suspected but not proved	15	8
No change in condition of the lens either observed or suspected	45	23

had not been confirmed on previous occasions In no case was complete re gression of the ASCV observed

Similar changes occurred also of posterior subcapsular vacuoles However the anterior and posterior lesions did not always undergo identical changes in some cases the ASCV regressed whereas concurrently the posterior subcapsular vacuoles progressed

4 The observations (i) that in many eyes the condition of the lens deteriorated after Phospholine Iodide withdrawal and (ii) that regression of cataractous changes characterized by ASCV was observed in some cases where the drug was not withdrawn gave rise to the question whether discontinuance of Pho spholine Iodide therapy actually prevents the development or progression of cataracts in patients who have been treated with the drug for six months or more

When it was suspected that Phospholine Iodide might be cataractogenic the drug was withdrawn wherever possible Assessment of the effect on the lens of discontinuing Phospholine Iodide therapy would have been facilitated if the material had been arranged for statistical analysis This was however not done for ethical reasons

An attempt was made to answer the above mentioned question as follows The 198 eyes in the total series treated with Phospholine Iodide for at least six months were grouped according to duration of treatment with the drug It was hoped that comparisons between groups of eyes treated with the drug for different periods might throw some light on the problems For instance A group of eyes treated with Phospholine Iodide for about one year and followed up for one year after the withdrawal of the drug was compared with another group of eyes treated with the drug for about two years The purpose was to investigate if the two groups differed in visual loss resulting from lenticular changes during the year following the first year of treatment However several factors which could not be taken into account in the analyses of the cases in creased the difficulties in interpreting the comparative results Consequently the material was not analysed statistically Hence the results obtained can only form the basis for the following clinical impression Discontinuance of Phospho line Iodide therapy after less than one year of treatment may prevent the de velopment or progression of cataracts in some cases On the other hand when this treatment has been given for longer than 15 months it appears doubtful whether withdrawal has this effect

Part B

Material and Methods

As previously mentioned this part summarizes the behaviour of the lenses in

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GLAUCOMA MIOTIC THERAPY AND CATARACT

VI Experimental studies on the guinea pig eye

BY

UNO AXELSSON

Introduction

Retrospective clinical studies show that echothiophate (Phospholine Iodide) and paraoxon (Mintacol) may be cataractogenic in man (*Axelsson & Holmberg* 1966 *Axelsson* 1968a b c) As it may be difficult to obtain conclusive evidence from such studies an experimental investigation was begun to induce cataract in guinea pigs by local application of these drugs

Guinea pigs have been used for various types of studies on experimental cataract, especially for investigating the relation between vitamin C deficiency and cataract *Monjukova & Fradkin* (1935) and *Ferrora* (1940) observed lens changes in guinea pigs deprived of vitamin C other investigators who made similar experiments e g *Bietti & Carteni* (1934) *Johnsson* (1936) and *Bellows & Rosner* (1937) were unable to observe any changes

2 4 dinitrophenol is cataractogenic in man but not in guinea pigs on a normal diet Dinitrophenol given per os induced cataracts in guinea pigs on a vitamin C deficient diet this applied also to injection of compounds related to dinitrophenol e g paranitrophenol (*Ogino & Yasukura* 1957)

Radiation produces cataract in the guinea pig whose lens is more susceptible to radiation injury than is the rabbit lens (*v Sallman et al* 1957)

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was due to cataract In no less than 78 eyes or 39 % of the total series dense or almost dense cataracts developed during the observation period So far cataract extraction has been performed in 48 eyes resulting in good vision in the majority of these cases

Summary

Part A of this paper describes the behaviour of the lens after discontinuance of Phospholine Iodide therapy in eyes with chronic simple glaucoma which had been treated with the drug for at least six months A total of 104 eyes were followed up for one year and 84 eyes for two years after withdrawal of Phospholine Iodide Progression of lenticular changes during the follow up period was mainly observed in eyes presenting the type of cataract characterized by anterior subcapsular vacuoles, and especially during the first follow up year On the other hand, in some cases there was evidence of regression of these changes This was particularly apparent during the second follow up year

Part B deals with the findings in 126 patients (198 eyes) with chronic simple glaucoma treated with Phospholine Iodide in various concentrations for at least six months The observation period was from six months to eight years There was evidence of increased cataract formation in 108 eyes (54 %) the majority of which had clear lenses or only minimal cataractous changes when treatment was begun In no less than 78 eyes (39 %) dense or almost dense cataracts developed during the observation period

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A. Experiments on long term basis

As in man topical use of Phospholine Iodide or Mintacol often induces cataract only after more than one year it was decided to extend these studies over a long period If no definite results were obtained within six months the intention was to investigate whether vitamin C deficiency or x radiation would make the treated lenses more susceptible to cataractous changes

In a preparatory study ten male pigmented guinea pigs average weight 300 g fed on the normal diet were treated with Phospholine Iodide Five were studied for more than two years two of these for as long as three years

During the preparatory study *bilateral* lens changes developed in some of the animals In order to ascertain whether such changes were influenced by Phospholine Iodide or Mintacol therapy a serial test of 36 pigmented and 36 albinotic female guinea pigs mean weight 300 g was made In each group of 36 animals 12 received Phospholine Iodide 12 Mintacol and 12 were untreated They were fed on the normal diet and were examined once or twice a month

After seven months there were 66 survivals which were divided into four groups for further study as described below In all the groups the animals continued with or without treatment as previously

Group I Six Phospholine Iodide treated three Mintacol treated and six untreated pigmented animals were given the vitamin C deficient diet They were examined at least twice a week All these 15 animals died between the 23rd and the 35th day of the experiment

Group II Six Phospholine Iodide treated six Mintacol treated and six untreated pigmented animals were given the vitamin C deficient diet for two weeks thereafter the normal diet for two weeks the vitamin C deficient diet for another two weeks etc Sixteen of these 18 animals were followed up for more than six months They were examined twice a month

Group III Six Phospholine Iodide treated six Mintacol treated and six untreated albinotic animals on the normal diet were exposed to x radiation In each group of six animals three received 500 r and three 750 r All the 18 animals were followed up for eight months and 12 for more than one year Examinations were made once or twice a month

Group IV Three Phospholine Iodide treated six Mintacol treated and six untreated albinotic animals on the normal diet served as controls

When these long term experiments had continued for two years the surviving animals were killed and the eyes of treated animals were enucleated for histological examination

The present experiments were performed on both a long term and a short term basis. This paper describes the various experiments and contains some observations of interest regarding the guinea pig lens.

Material and Methods

Both pigmented and albinotic guinea pigs were used. The normal diet consisted of hay, oats, carrots, water ad lib and green grass when available. In some experiments a vitamin C deficient diet of the following composition (in weight %) was given: Barley grits 20.0, white oat grits 18.0, wheat bran 17.0, soya meal 17.2, fish protein 5.1, wheat straw 25.0, baking yeast 0.5, trace elements 1.0, NaCl 0.2 and vitamin mixture without vitamin C 1.0. This diet was tested in the following way.

Five pigmented and five albinotic guinea pigs of varying ages had their left eyes punctured and the aqueous humor removed. Its content of ascorbic acid as determined by the method of *Harris & Olliver* (1942) was 5.3 ± 0.8 mg %. After two weeks on the vitamin C deficient diet the right eyes were punctured and the ascorbic acid content of the aqueous again determined. In eight animals no indophenol reducing substance was found; in the other two it was 0.1 and 0.2 mg % respectively. All ten animals continued on the diet but five were injected with 10 mg vitamin C daily. The latter animals all remained in good condition whereas the other five died between the 22nd and the 31st day of the experiment with the clinical picture of scurvy.

Miotic treatment was given to the left eye once daily except Sundays, the right eye serving as control. Phospholine Iodide in 0.25 % solutions or Mintacol Solubile in 3 % solutions (= Mintacol 1:2000) were used.

Roentgen radiation was delivered by a Muller Rt 200 apparatus. Only the head was irradiated. The radiation factors were: 180 kv, 20 ma, 89 r/min, 0.5 mm Cu plus 1 mm Al filtration, Tsd 40 cm, field 6 × 8 cm.

For slit lamp examination of the lens the pupil was dilated as a rule by instillation of an 0.5 % or a 1 % solution of Mydriacyl*)

For histological examination the lens was removed from the eye using a dissection microscope. The lens and the anterior segment of the eye were fixed separately in a 10 % neutral formalin solution, embedded in paraffin, sectioned and stained (hematoxylin eosin, van Gieson and PAS). Iris specimens from pigmented animals were depigmented before staining.

*) Mydriacyl = tropicamide (Alcon, U.S.A.)

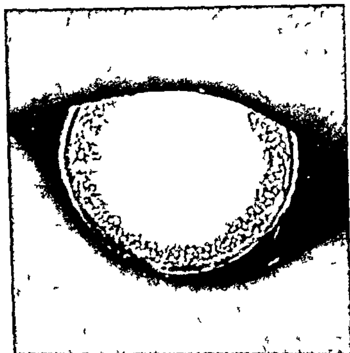


Fig 1
Pronounced erupti n of the large vacuoles

vacuolated cataract respectively The latter type was first seen in animals of both sexes aged 3 4 months but more frequently in the albinos about one in four The earliest changes consisted of a peripheral corona or peripheral clusters of densely packed small subcapsular vacuoles located both anteriorly and posteriorly During the next few weeks the vacuoles increased in size and became irregular In pronounced cases a broad zone of the lens was vacuolated (fig 1) After this stage the course of events differed In some cases the vacuoles entirely disappeared leaving no opacities In other cases a larger or smaller number of vacuoles attained a milky appearance resembling the coronary cataract in man In other cases the vacuoles seemed to rupture or become compressed and caused various types of cortical opacities which in time were displaced deeper into the lens (fig 2)

In many animals new vacuoles appeared 3 5 months later In some cases the vacuoles again disappeared whereas in other cases a new layer of various cortical opacities was formed (fig 3) Up to five eruptions were observed in one and the same animal But dense cataracts never developed

The small vacuolated cataract was first seen in animals aged 6 8 months

Table I

Miotics (to left eye) diets and daily doses of subcutaneously administered paranitrophenol given to the various groups in the short term experiments

Group	No animals	Miotic	Diet	Paranitro phenol
1	5	Phospholine	Vit. C deficient	2 5 mg
2	5	Phospholine	Vit C deficient	5 mg
3	5	Mintacol	Vit. C deficient	2 5 mg
4	5	Mintacol	Vit. C deficient	5 mg
5	5	Phospholine	Vit C deficient	–
6	5	Mintacol	Vit. C deficient	–
7	5	Phospholine	Normal	–
8	5	Mintacol	Normal	–

B Experiments on short term basis

The aim of the experiments was by frequent examinations to ascertain whether local application of Phospholine Iodide or Mintacol (i) gives rise to transient lens changes in guinea pigs on a normal or a vitamin C deficient diet or (ii) accelerates the cataract which according to *Ogino & Yasukura* (1957) can be induced in guinea pigs depleted of vitamin C by injections of paranitrophenol

Forty male pigmented guinea pigs average weight 300 g were divided into eight groups and given miotics diets and subcutaneous injections of paranitro phenol as shown in Table I They were examined every or every second day All animals on the vitamin C deficient diet died under the clinical picture of scurvy between the 14th and the 35th day of the experiment

Results

As mentioned above spontaneous lens opacities developed in these series of guinea pigs Since such opacities have to be taken into account in a study on experimental cataract they will be briefly described

Congenital cataracts most often bilateral and situated in or around the foetal nucleus are common but do not change with time Small round opacities of varying size in connection with the sutures are also common at birth and are subsequently seen to develop in animals of all ages

Of greater interest are two types of cataracts which always occurred symmetrically in both eyes and which will be referred to as the small and the large



Fig 4
The small vacuolated cataract

The initial changes appeared in the lens equator as a thin border of very small vacuoles of equal size in oblique illumination seen as silky spots During the next year the vacuoles increased in number but not in size forming a more or less dense and broad ring like opacity (fig 4) If these small vacuoles appeared in eyes with the large vacuolated cataract they often were arranged in rows like the spokes of a wheel (see fig 2) The small vacuolated cataract was observed in about 80 % of both pigmented and albinotic guinea pigs more than six months old

It should also be mentioned that anterior cortical opacities developed in connection with infected corneal ulcers which are common in guinea pigs

A. Observations on the long term studies

1 Prolonged topical use of Phospholine Iodide or Mintacol up to three years did not injure the lenses of guinea pigs on a normal or on a vitamin C deficient diet Nor did it initiate or precipitate spontaneous lens opacities Lenticular changes attributable to vitamin C deficiency were not observed



Fig 2

Perinuclear opacity resulting from an eruption of the large vacuoles The thin radiating spokes best seen between 1 and 5 o clock consist of small vacuoles

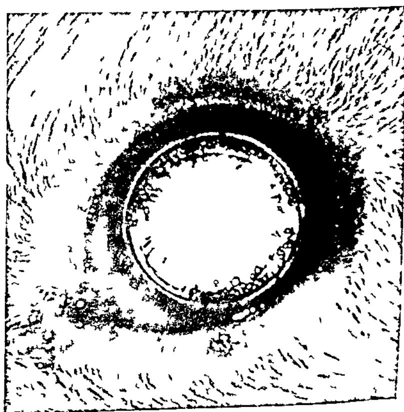


Fig 3

... which is the

the cataractogenicity of such drugs However it may be suspected that the opacities observed by Diamant were of the above mentioned type Thus they were located in the anterior central portion of the lens and were observed in severly affected animals or in those which had died In the surviving animals the opacities as a rule subsided In the present study clouding of the type discussed was observed in some severly scorbutic animals which had ceased blinking and in many dead animals especially in eyes which were kept open and had a shallow anterior chamber These opacities however were in no way related to the miotic treatment given Thus the observations made by Diamant hardly prove that anticholinesterase drugs are cataractogenic in guinea pigs

Nor does the present study afford any evidence that such is the case This however does not contradict the view that anticholinesterase drugs are cataractogenic in man Hitherto no drug considered to be cataractogenic in man has been shown to induce cataracts in all animal species used in experimental cataract work

An interesting and important result of these studies on guinea pigs is the observation of spontaneously occurring lens changes especially those referred to as the small and the large vacuolated cataract respectively

In previous experimental reports lenticular changes probably the small vacuolated cataract are described *Monjukova & Fradkin* (1934) in their description of the cataract considered to be related to vitamin C deficiency mention that besides changes in the posterior lens there appeared a girdle of punctate opacities in the cortical layers" *Upton et al* (1956) in their studies on radiation cataract in different species observed a steamy haziness of the lens in conjunction with the appearance of the early posterior polar opacities in the animals exposed at the highest doses This results from the formation of microscopic subcapsular vacuoles in both the anterior and the posterior regions of the lens producing a ring like opacity at the equator This opalescent appearance was observed in all three species but was more pronounced in guinea pigs and to a lesser extent in rats

The large vacuolated cataract resembles the experimental cataract in rats which *Buschke* (1943) calls the diabetic type because it appears as a result of diabetes and after administration of lactose galactose and fructose It also resembles the early stages of toxic cataract as described by *Bellows* (1963)

As far as we are aware no description of the normal ageing of the guinea pig lens has been given in the literature Consequently it is not possible to decide if the opacities observed are to be considered as a normal occurrence Whether or not this is the case will not be discussed here It should only be pointed out that these opacities were observed in guinea pigs derived from different strains and bred under ordinary laboratory conditions Animals showing these lens changes did not in any other respect differ from animals with clear lenses

2 Five months after the radiation small granular opacities and elongated vacuoles were seen in the posterior subcapsular region especially along the suture in the lenses of two animals exposed to 750 r One month later all albinotic animals were examined according to a blind technique The lens changes described were observed in six animals all exposed to 750 r and were therefore interpreted as x-ray cataract

Eight months after radiation these changes were observed in all animals exposed to 750 r in six exposed to 500 r but in none of the controls However, asymmetry between the eyes treated with miotics and the control eyes regarding the extent and degree of opacification was not observed in any animal, or in those followed up for more than one year

3 On histological examination there was no difference between the treated and the untreated lens in any animal

4 After 8 10 months of miotic therapy a peculiar pupillary reaction was observed in many animals especially in those treated with Phospholine Iodide Instillation of the miotics used caused only semi miosis and after about 12 hours the pupil of the treated eye was dilated as compared with that of the untreated eye reacting poorly or not at all to light Normally the miotics produced good miosis persisting for up to 12 hours After discontinuing the therapy in some animals this phenomenon gradually became less pronounced but had not disappeared when the animals were killed two months later On histological examination there were no signs of atrophy or vascular damage of the irides of animals with this abnormal pupillary reaction

B Observations on short term studies

1 Topical Phospholine Iodide or Mintacol did not produce transient lens changes in guinea pigs on a normal or on a vitamin C deficient diet

2 Subcutaneous injections of paranitrophenol did not induce cataracts in guinea pigs depleted of vitamin C

Discussion

Systemic administration of large doses of morphine like drugs catechol amines or chlorpromazine induces acute reversible anterior lens opacities in small rodents *Fraunfelder & Burns* (1966) showed that no opacities occurred in mice if the lids were kept closed and suggested that the cause of drug induced cataract is evaporation of water through the cornea due to reduced blink rate *Diamant* (1954) observed lens clouding in guinea pigs after intracarotid injections of various anticholinesterase drugs which is often quoted as a proof of

the cataractogenicity of such drugs However it may be suspected that the opacities observed by Diamant were of the above mentioned type Thus they were located in the anterior central portion of the lens and were observed in severly affected animals or in those which had died In the surviving animals the opacities as a rule subsided In the present study clouding of the type discussed was observed in some severly scorbutic animals which had ceased blinking and in many dead animals especially in eyes which were kept open and had a shallow anterior chamber These opacities however were in no way related to the miotic treatment given Thus the observations made by Diamant hardly prove that anticholinesterase drugs are cataractogenic in guinea pigs

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The observation of this high incidence of spontaneously occurring lens changes in guinea pigs stresses the importance of adequate control series whenever this animal is used for experimental cataract studies

Summary

This study was undertaken to induce cataracts in guinea pigs by topical use of anticholinesterase drugs Prolonged *instillation of Phospholine Iodide or Mintacol* even up to three years did not cause any type of lens opacity or initiate or precipitate spontaneously occurring opacities X radiation or vitamin C deficiency *did not* seem to make the guinea pig lens vulnerable to cataractous changes by Phospholine Iodide or Mintacol therapy

Acknowledgements

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VARIA

International Council of Ophthalmology

The International Council of Ophthalmology met on 23rd April 1969 in Athens under the presidency of Prof Charamis The Gonin medal was awarded to Prof Meyer Schwickerath The Council undertook the organization of the XXI International Congress of Ophthalmology in Mexico the study of information in ophthalmology and the preparation of a perforated card for the Coding System of eye disorders the standardization of tonometers and the problem of contact lenses for which a committee has been appointed

Professor J François
Secretary of the Council

ACTA OPHTHALMOLOGICA VOL. 47 1969

From the Department of Experimental Ophthalmology
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ON THE REGULATION OF THE INTRAOCULAR PRESSURE

BY

C. E. T. KRAKAU

Introduction

In order to be able to work optimally the biological systems strive for peace. Le milieu interne, as Claude Bernard put it, should be kept constant in different respects. The stability of the internal environment is spoken of by Cannon as homeostasis.

Homeostatic mechanisms may vary considerably in kind and complexity. A simple thermal isolation or a buffer may fulfill homeostatic functions. More advanced control mechanisms however incorporate an important principle, namely a feed back loop. This means that the controlling system senses some quality, pressure, temperature, pH etc. and leads the result of its investigation back to and controls the effector organ of the quality in question.

It is well established that blood pressure, heart activity, respiration, voluntary muscular activity and many other things where precision and constancy are required are carefully governed by feed back mechanisms. The intraocular

The Danish Ophthalmological Society has entrusted me to give the Bjerrum lecture for 1968 and I feel it *a very great honour to have this opportunity* to adress this learned society. The name Bjerrum is inextricably connected with the large field of our discipline that concerns the glaucoma disease. It is therefore appropriate, I believe, to chose a topic within this scope. The special aspect of glaucoma I wish to concentrate on is the technological one, because I have a feeling that, however inadequate our mathematical models may be, it may be stimulating to reflect on these problems in terms of control theory.

Bjerrum Memorial Lecture in the Danish Ophthalmological Society on December [illegible] th 19[illegible]

pressure is kept practically constant for decades – if all goes well – and we would have ex analogia reason to be astonished if this were not due to well designed control mechanisms

Although physiologists have long been aware of the importance of control mechanisms it is the interest of technologists in regulated systems that has led to the establishment of a well developed theory which enables us to tackle problems of this kind in accurate terms

It is customary to speak of systems which thus contain controlling and con trolled elements and which receive ingoing signals (input) and emit out going ones (output) In particular we speak of *servo systems* when the system is expected to make the output follow the input as closely as possible An example the eye movements when the flight of a bird is followed A *regulator* system on the other hand is a system the output of which has been kept as constant as possible in spite of miscellaneous disturbances An example tem perature regulation in the body

Feed back

In order to illustrate the important idea of feed back, let us look at a machine where a feed back was used probably for the first time in the annals of tech nology It is the steam engine of Watt (Fig 1) which has a speed controlling governor If the engine for some reason (such as lowered load) increases its speed the governor top (Fig 2) will rotate faster too The centrifugal forces will draw the balls outward and by means of levers a valve throttles the steam As a result the engine returns to a lower speed This is a feed back since the velocity of the main axis controls the steam influx and thereby adjusts the speed

Another more commonplace regulator is a thermostat The controlling ele ment is a thermometer which feeds back its information to the heating body which in turn is controlled

The light pupillary reflex is a thoroughly familiar biological example of a feed back system As we know an increase in light influx through the pupil reduces its size and thereby the quantity of light falling on the retina The feed back loop consists of the nerve fibres in the optic tract mesencephalic cen tres and the oculomotor nerve

Transient analysis

The technician is usually faced with problems of the type Construct a regula ting system which fulfils certain prescribed requirements The problem of the physiologist is more often of the type Make an analysis of a system and for mulate a mathematical model which satisfactorily describes that system The

MACHINE À VAPEUR.

Fig 1
Steam engine with Watt's governor

Fig ⁹
Centrifugal governor

system is considered a black box (Fig 3) the input of which can be chosen to some extent arbitrarily and the output of which can be recorded In other words we determine how a signal of a known shape is modified by the system



Fig 3
Black box*

so that the system can be characterized and may also yield some hints on a plausible construction If possible an input signal of a kind easily tackled mathematically, such as an impulse "function" or a step function is chosen (Fig 4) (It is not however a prerequisite to use such functions) This approach is used in so called transient analysis since the part of the response which tends towards 0 with time (the transient) is analysed The rest of the response which does not tend towards 0 is called the steady state It informs us about the error of regulation but does not say anything about the dynamic properties of the system

Another approach different in principle is frequency analysis which uses a

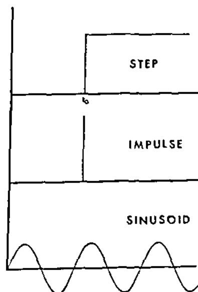


Fig 4

Step function defined by $\begin{cases} y = 0 & t < t_0 \\ y = A & t \geq t_0 \end{cases}$

Impulse function $\int_{-\infty}^{\infty} \delta(t)\, dt = 1 \quad \delta(t) = 0 \text{ if } t \neq t_0$

Sinusoid $y = A \sin \omega t$

purely sinusoidal input The amplitude and phase relations of the forced response are the interesting magnitudes in this analysis not the transient response. The latter type of analysis seems to be difficult to apply to the systems we are going to deal with and we shall confine ourselves to transient analysis

Two simple flow models

Consider a very simple system of great interest to us It is the flow of a fluid through a resistance The set up shown in Fig 5 is completely unrealistic Its walls are absolutely rigid The pump delivers a flow F_0 At the cock there is a resistance R (no resistance in other parts of the system) The pressure inside the ball is I_0 the pressure difference over the cock is P_0 P_v If the flow is suddenly increased with F_1 and R is kept constant the pressure is increased equally promptly

In Fig 6 the model has been changed slightly The walls are no longer completely rigid but elastic In the beginning we have a steady state with constant flow and pressure Suddenly the flow is increased as before but we find that the pressure gradually reaches a steady state It takes a little time to blow up the ball which has a greater volume at the higher pressure The simple formula

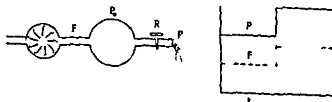


Fig 5
Rigid flow model

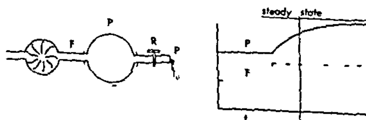


Fig 6
Flow model with elastic walls



Fig 3
Black box

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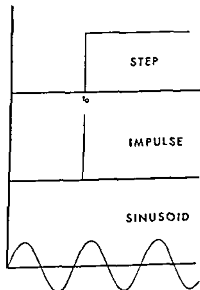


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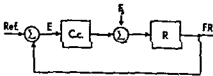


Fig 8
Flow model with regulation Reference pressure minus actual pressure gives th error signal (E) which regulates the pump

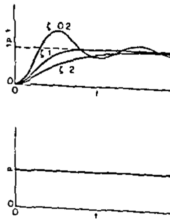


Fig 9
Response to step funct on in second order system

$$F = \frac{P_o - P_v}{R} \quad (1)$$

has to be completed with a term dV/dt i e the part of the flow from the pump which is required to inflate the ball This situation is similar to a perfusion of an enucleated eye For a bulb we find from Friedenwald s tables that it is clear that in a moderate pressure range there is a practically linear relationship between pressure and volume of the bulb If the bulb is inflated by 1 mm³ when the pressure is 16 mm Hg and the increase about 0 8 mm Hg an inflation of 2 mm³ doubles the pressure increase Then we may write dV/dt = dP/dt k where k is a constant Thus

$$F_o + F_s = F_t = \frac{P}{R} + k\frac{dP}{dt} \qquad P_o - P_v = P \quad (2)$$

Solving this 1st order diff equation gives $P(t) - P(O) = F R (1 - e^{-\frac{t}{kR}})$ (3) where P(O) and P(t) are taken at times O and t after the start of F

A step shaped increase of F gives an increase in pressure which exponentially approaches a new steady state as drawn in Fig 6 We have obviously introduced a time dependence which makes it necessary to be careful not to treat transients as steady states

Flow diagram

A practical mode of representation is the flow diagram Boxes are used to denote some operation on an input (multiplication derivation etc.) Circles are used at points where components add or subtract lines and arrows signify the direction of the flow One way of drawing a flow diagram for equation 2 is shown in Fig 7 F_o which is the initial flow is put constant and F is the extra flow A feed back loop takes back the information about the pressure P This information is processed (differentiation and multiplication by a constant) and the result is subtracted from F_t The steady state obviously is the same as in the first rigid case Thus the presence of a feed back loop does not necessarily

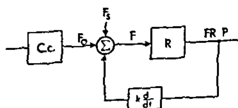


Fig 7

Flow diagram of model in Fig 6 The elastic effects are mediated by the loop

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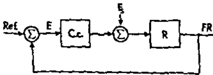


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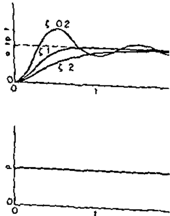


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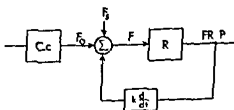


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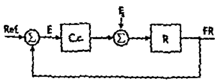
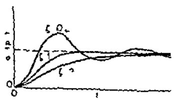


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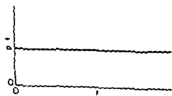


Fig 9
Response to step function in second order system

function of a 2nd order system By choosing different damping factors the response may show more or less pronounced oscillations or a damped simple curve When the damping factor is great the response approaches a simple logarithmic damping

The places where a regulating mechanism might be effective in the simple system of Fig 6 are easy to indicate It might be sensible to let the pump work less if the pressure is increased or to open the cock a little In the eye this means that the ciliary body ought to diminish its production of aqueous or the trabecular resistance decreases or/and new outflow ways are opened These are trivialities to every eye doctor The flow diagram (with all reservation for in completeness) may be drawn as in Fig 10

Just as in the technical cases it is difficult to arrange an efficient regulation without some sort of reference an idea of the correct pressure somewhere From receptors or other devices messages have to be given about the actual pressure and the difference actual minus ideal pressure (= the error signal) influences the sensitive structures in a presumably normalizing direction Nothing is known about the function of the error signal which influences the effector side It may be some derivative integral of the error or a combination of these or even more complicated nonlinear functions However it is usually sufficient to assume as a hypothesis a model of modest complication Already the 2nd order system with its rich variational possibilities may be a satisfactory approximation of the behaviour of the system at least within a modest range

The steps of the black box investigation will be then collecting experimental data for input and output (such as flow or resistance and pressure) than calculating the parameter values of the model which for a certain input gives an output similar to that experimentally obtained If it turns out to be impossible to get a proper adjustment with a 2nd order model more complicated

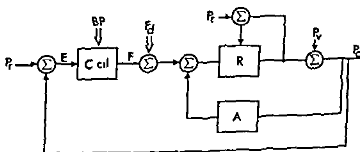


Fig 10

Hypothetical flow model for regulation of the intraocular pressure Error signals affect the ciliary body and the outflow resistance A represents elastic effects P_v venous pressure BP blood pressure influencing the ciliary body F_t flow by perfusion of the ant chamber

ones have to be tried Analog computers may be of considerable help in this calculation where the system is simulated with electronic components

In practice it is often not possible to attain a step or impulse function as input but only some more rounded or smoothed curve or as in Fig 11 a series of values on such a curve The first step will then be to find a so called weight ing function which connects input with output Then a step input can be given to the model found and a response is then obtained which can be compared with that from a model with other parameter values In other words the answer of different systems to exactly the same loading can be determined Problems like differences in behaviour between normal and glaucomatous eyes can be treated Is for instance a steady state obtained after much the same time in different eyes and are there any differences in the efficiency of regulation?

Our investigation of the black box however penetrating does not say any thing about the construction of the mechanisms involved The regulation if there is any can take place by means of nervous reflex arcs or hormonal in fluences but also by local influences such as pressure sensitive valves and other simple physical mechanisms

Since our formulae do not make any distinctions between these devices it seems convenient to define a regulatory mechanism in a wider sense than is customary among physiologists When a change of input causes a change of

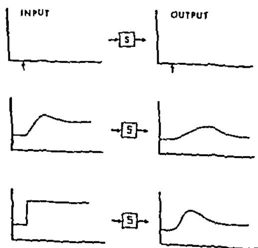


Fig 11

a Experimental data.

b Continuous function input to model giving approximatively the same output as the system

c Step input to model

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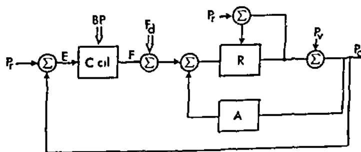


Fig 10

Hypothetical flow model for regulation of the intraocular pressure Error signals affect the ciliary body and the outflow resistance A represents elastic effects P_v venous pressure *BP* blood pressure *influencing the ciliary body* F_d flow by perfusion of the ant chamber

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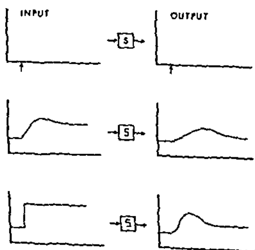


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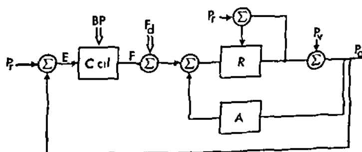


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Diurnal variations of T and F have been treated by Ericson (8) using the suction cup method of Rosengren According to his measurements the flow is reduced in man during the night to about 1/3 of the day value The IOP varies modestly and a compensatory increase of the outflow resistance during the night has to be presumed It would be of great interest to have these important results confirmed with other techniques

The results of these groups of investigations are on the whole in agreement a reduction of the flow leads to a compensatory increase of resistance Reason ing teleologically there seems to be a tendency to keep the IOP constant in spite of a diminished secretion of aqueous Most of the investigations are based on tonography where the resistance has been measured after some kind of load ing on a single occasion in the hope that the steady state has been reached

Perfusion on enucleated eyes Many experiments have been performed on enucleated eyes and with the perfusion technique it has been found that the resistance depends on the IOP As a rule an increased perfusion pressure cau ses an increase in resistance That means rather an antiregulating mechanism It is not difficult to raise objections to these scarcely physiological experiments which seem to have little bearing in this connection Their importance lies in pointing out a possible mechanism for an irreversible blockage of the chamber angle at very abnormal pressures

Influence of pressure on the production of aqueous With his fluorometric technique Goldmann (9) has shown that the flow is abnormally low in eyes with open angle glaucoma The pressure increase in the glaucomatous eye is some what reduced by this reduced flow This observation is further supported tono graphically by i a Weekers and Prijot (10)

On the experimental side we have Bárány s works on pseudo facility a con cept introduced by him (11) In tonography one generally reckoned with the production of aqueous being continued irrespective of the loading of the eye This seems however not to be *true* There is a reduction of the inflow or a reab sorption of fluid over the capillary walls by an amount corresponding to 20 per cent of the total facility (normal human subjects) (Kupfer and Sanderson (12)) The results is an overestimation of facility of outflow In the wide sense this should be considered a regulatory *mechanism*

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Experimental evidence of an IOP regulation

Influence of aqueous production changes on outflow resistance

There have been several attempts to establish the existence of a control mechanism for the IOP and we will now try to fit them into the flow model of Fig 10 As a first group we consider those investigations where the aqueous production has been influenced by various means The effect of the feed back loop at the ciliary body is obscured (Fig 12) The change in IOP and that in outflow resistance have usually been recorded A pioneer work in the search for regulating mechanisms has been made by Ernst Barany In 1947 Barany performed a series of rabbit experiments in which the carotid artery was occluded unilaterally (1) The IOP was restored to normal values earlier than the blood pressure In a later series the investigation was followed up by determinations of the outflow resistance (perfusion) The resistance was found to have increased by about 9 per cent 6 days after the occlusion (2)

In a number of investigations the production of aqueous has been diminished by means of chemical agents Becker (3) showed tonographically in rabbit that the pressure reduction after Diamox is often partially masked by a compensatory increase in resistance Similar results were obtained in humans Prijot and Lavergne (4) put the compensatory increase in resistance at 17 per cent There are other remedies (vasopressine chloropromazine) which reduce the production of aqueous up to 60 per cent Here too the effect on the eye pressure is

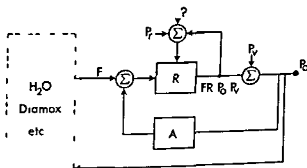


Fig 12
Disturbance of aqueous production Effect of the loop to the ciliary body not discernable

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There have been several attempts to establish the existence of a control mechanism for the IOP and we will now try to fit them into the flow model of Fig 10 As a first group we consider those investigations where the aqueous production has been influenced by various means The effect of the feed back loop at the ciliary body is obscured (Fig 12) The change in IOP and that in outflow resistance have usually been recorded A pioneer work in the search for regulating mechanisms has been made by Ernst Bárány In 1947 Bárány performed a series of rabbit experiments in which the carotid artery was occluded unilaterally (1) The IOP was restored to normal values earlier than the blood pressure In a later series the investigation was followed up by determinations of the outflow resistance (perfusion) The resistance was found to have increased by about 9 per cent 6 days after the occlusion (2)

In a number of investigations the production of aqueous has been diminished by means of chemical agents Becker (3) showed tonographically in rabbit that the pressure reduction after Diamox is often partially masked by a compensatory increase in resistance Similar results were obtained in humans Prijot and Lavergne (4) put the compensatory increase in resistance at 17 per cent There are other remedies (vasopressine chloropromazine) which reduce the production of aqueous up to 60 per cent Here too the effect on the eye pressure is

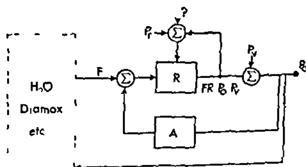


Fig 12
Disturbance of aqueous production Effect of the loop to the ciliary body not discernable

diminished however by a compensatory increase in resistance (Constant and Becker (5)) de Roeth (6) showed tonographically that an increase in the osmotic pressure of the blood reduces the formation of aqueous and increases the out flow resistance When it comes to osmotic hypotoni of the blood as in the water provocation test opinions differ An increased flow is generally presumed Becker (7) claims that the resistance sometimes also increases (determined to nographically) We will return to this question below

Diurnal variations of T and F have been treated by Ericson (8) using the suction cup method of Rosengren According to his measurements the flow is reduced in man during the night to about 1/3 of the day value The IOP varies modestly and a compensatory increase *of the outflow resistance during* the night has to be presumed It would be of great interest to have these important results confirmed with other techniques

The results of these groups of investigations are on the whole in agreement a reduction of the flow leads to a compensatory increase of resistance Reason ing teleologically there seems to be a tendency to keep the IOP constant in spite of a diminished secretion of aqueous Most of the investigations are based on tonography where the resistance has been measured after some kind of load ing on a single occasion in the hope that the steady state has been reached

Perfusion on enucleated eyes Many experiments have been *performed* on enucleated eyes and with the perfusion technique it has been found that the resistance depends on the IOP As a rule an increased perfusion pressure cau ses an increase in resistance That means rather an antiregulating mechanism It is not difficult to raise objections to these scarcely physiological experiments which seem to have little bearing in this connection Their importance *lies in* pointing out a possible mechanism for an irreversible blockage of the chamber angle at very abnormal pressures

Influence of pressure on the production of aqueous With his fluorometric technique Goldmann (9) has shown that *the flow is abnormally low* in eyes with open angle glaucoma The pressure increase in the glaucomatous eye is some what reduced by this *reduced flow This* observation is further supported tono graphically by i a Weekers and Prijot (10)

On the experimental side we have Bárány s works on pseudo facility a con cept *introduced by him (11) In tonography* one generally reckoned with the production of aqueous being continued irrespective of the loading of the eye This seems however not to be true There is a reduction of the inflow or a reab sorption of fluid over the capillary walls by an amount corresponding to 20 per cent of the total facility (*normal* human subjects) (Kupfer and Sanderson (12)) The results is an overestimation of *facility* of outflow In the wide sense this should be considered a regulatory mechanism

output which in a steady state is less than if the system had been independent of output a regulation in the wide sense prevails If F is say doubled and the steady state of $P_o - P_v$ is only 1 5 times (and not twice) as high as before something like a regulation has occurred to R Further analysis in case a regulation is suspected makes it as a rule necessary to break feed back loops in the system.

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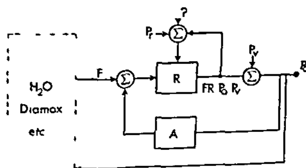


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constant An investigation of Bárany (16) should be recalled here A regulating system attributed to osmotic forces and acting primarily on the flow and not on pressure was described Evidently a working hypothesis on the intraocular pressure regulation has to be formulated in very general terms

Intraocular nerve fibres

The eye has abundant sympathetic and parasympathetic nerves In man Ehinger (17) failed to find sympathetic nerves in the scleral trabecular meshwork. The nerves found in this region must consequently be parasympathetic or possibly sensory The ciliary body and the iris *like the small vessels are well* equipped with sympathetic nerves (17) which are strategically placed for regulating cocks in the system According to several works i e by Davson and Matchett (18) Greaves and Perkins (19) the sympathetic nerve system probably mediates decreases in the IOP In perfusion experiments Langham (20) has shown that the regulation mechanisms of rabbits are considerably reduced if preganglionary sympathetic fibres are severed

Central influences

Experiments performed with stimulation of various areas in diencephalon (von Sallman and Lowenstein (21) Gloster and Greaves (22)) show that changes of the IOP without general effects on the blood pressure can be obtained probably by some vascular influence The physiological importance of these stimulations is still unclear The effect of narcosis on the IOP indicates a central influence At narcosis obtained with a variety of preparations (ether barbiturates etc) there is a pressure reduction of about 6 mm Hg (Kornbluath et al (23)) The effect is claimed to depend on a reduction of the resistance and only to a minor extent on decreased muscular tone

Requirements of methods for studies of regulatory mechanisms

No doubt there is evidence of a regulation of the IOP though the results are not such as to permit a satisfactory analysis This is not astonishing when we consider the difficulties of the measuring situation More than in most other physiological work it is essential not to disturb the variables to be measured by the mode of observation itself Thus as has been mentioned narcosis for instance reduces the pressure and abolishes the vegetative reflexes The pupillary reflex is the lodestar for the narcotiseur But narcosis is inevitable in most experimental work with animals In a recently published investigation Marre (24 25) strongly stressed this point In a series of rabbit experiments Marre made perfusions through a cannula in the anterior chamber without narcosis The

The possibility of a regulating loop controlled by the venous pressure might be of importance and must also be mentioned The venous pressure is an unpleasantly hazardous parameter It seems to be difficult to measure it in a meaningful way since it changes from one episcleral vein to another and also varies considerably with time depending on respiration strain etc The assumption of a constant venous pressure may be too great a simplification since its range of validity has not been tested Further according to some recent experiments by Barany (13) the venous pressure seems to influence the outflow resistance An increased venous pressure may under certain circumstances reduce the resistance It is at present difficult to estimate the importance of this factor

Receptors

When we turn our attention to morphological support for regulatory mechanisms in the first place pressure-sensitive receptors we find that in the eyes of higher animals they are rare if not completely absent The nearest thing seems to be those found by Vrabec (14) in the goose eye but the goose seems rather distantly related to man But do we really have to look for receptors of the pressure sensitive kind?

As we know the receptor begins firing action potentials eagerly when a step stimulus is started But in spite of constant stimulus intensity the frequency of potentials diminishes and after some time it is back to a resting level This adaptation of the receptor must raise considerable constructional difficulties if used in a control mechanism This drawback is reduced however if there is a local reference signal Then we are dealing with zero adjustment of an error signal in a time dependent system Unfortunately a pressure norm is hardly to be found in the eye However the parameter which is primarily regulated might be not the pressure itself but some other quality dependent on pressure Most likely some factor like pH pCO etc changes in the eye secondary to the pressure For many chemical qualities there is a reliable and well buffered reference in the blood A chemoceptor feeling the difference of some chemical factor inside and outside for instance a blood vessel could no doubt give information on the circulation of aqueous Further the chemoceptors generally have considerably longer time constants than have the pressure sensitive elements which make them better suited to control systems

However speculative these considerations may be they are not completely without experimental support In an investigation on rabbits Perkins (15) succeeded in recording action potentials from the long ciliary nerves as a response to a raised intraocular pressure But the responses were transitory if the pressure was kept constantly elevated the nervous activity disappeared in about 10 sec Such responses as Perkins remarks are hardly suited to keeping the IOP

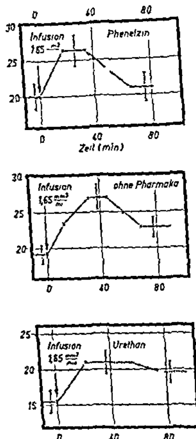


Fig 14

Infusion experiments of Marré showing deficient regulation under narcosis and improved regulation after centrally stimulating agent (Phenelzin)
By courtesy Dr E. Marré and Springer Verlag Heidelberg

In short there is no doubt that the analysis of regulatory mechanisms is intimately linked with the problem of finding improved methods

A few results with pupillary flow measurements

The procedure for pupillary flow measurements described in principle by Holm and Krakau (29) is not free from defects however it is still feasible that its application to regulatory problems may become fruitful

It permits us to make repeated flow determinations during a period of say 90 150 min Regretably pilocarpin has to be used since a miotic pupil is a pre

IOP was measured at short intervals and Tyrode solution was injected at a constant velocity from time to time Fig 13 shows a typical course for the pressure curve When the injection is started the pressure rises and reaches a maximum after 40 60 min Then a falling trend follows A steady state is not reached in the illustration rather one receives the impression that the pressure will remain above the starting pressure but will be lower than if R had been constant Under narcosis the regulatory effect is considerably smaller (Fig 14)

This is an experiment with a step function input (namely the infusion rate which in a transient analysis perhaps might be well approximated by a 2nd order system model (See Fig 10 where F_d is the extra flow) However the experiments are open to some objections The rabbit eye has the unfortunate habit of giving a trauma reaction after even very small traumata such as perfusion (Larsson (26) Sears (27) Dyster Aas (28)) Without checking the aqueous flare one cannot exclude the fact that such effects must have disturbed the experiment The analysis of the experiment is not very simple As may be seen from Fig 10 an influence on both the outflow resistance and the ciliary body by the induced pressure increase is possible The output input relation may be satisfied by the feed back acting on R or that influencing the flow or by a mixture at unknown proportions of both of these

Another prerequisite for an appropriate presentation of input and output is obviously that iterated measurements are obtainable – without traumatisation In this respect for instance the applanation tonometry is satisfactory for obtaining IOP But we need determinations of flow or of resistance and for this purpose tonography and most flow methods are hardly satisfying Besides its well known errors it is impossible to repeat this investigation very often in succession For obvious reasons the method should be applicable to human eyes

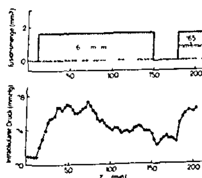


Fig 13
Infusion experiment of Marré (24)
By courtesy Dr E Marre and Springer Verlag Heidelberg

the accepted normal range If the venous pressure is presumed to be 8 10 mm Hg however we have to presume a change in resistance (higher resistance at lower pressure) in accordance with some findings quoted earlier

Fig 16 shows a pupillary flow/intraocular pressure diagram of a number of glaucomatous and glaucoma suspect eyes all on pilocarpine medication The flow values tend to be reduced at high pressures in accordance with Goldmann s findings previously mentioned

An experiment which seems to be well suited for a study of regulating me chanism is the water provocation test This test is widely used as an aid for establishing the diagnosis of glaucoma simplex in suspect cases Norskov (34) who recently published a large material of patients subjected to the test stres ses that in spite of its limitations it is still the best available test for this pur puse One litre of water (or 14 ml/kg body weight) is given to the patient over a period of 5 min and the IOP is followed with short intervals during 1½ hours If the pressure rises more than 8 mm Hg (the conventions vary some what) the glaucoma diagnosis is more probable The reason for the pressure increase is not fully understood but is generally presumed to be due to an increase in the aqueous produc ion or an increased transfer of water over the iris membranes P has also described an increased outflow resistance (apart from an increased secr ion)

In accordance with the theory of a pressure regulation we could expect the

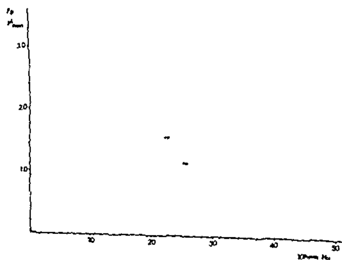


Fig 16
Flow and IOP (susp glauc. ● glaucoma spl ○)

requisite This is a drawback of unknown weight since it may be that some part of the regulating range of outflow resistance is taken into account by the artificial miosis

(The practical procedure of the method was demonstrated in a cinematographic film Since it has also been described at length in a paper by Holm and Wiebert (30, 31) its particulars are passed over here)

The method was first applied to a study of the effect of diamox on the flow of aqueous (Holm and Wiebert (32)) Though the predominant opinion on the mechanism of diamox is that the production of aqueous is reduced it is also claimed that its effects are due to vascular and other influences (the Maren survey (33))

Diamox was given in one series of experiments perorally in another intravenously In both series both IOP and flow were reduced In Fig 15 are plotted the flow and pressure values before and after administration of diamox In most cases these parameters are changed in a way which is consistent with a constant resistance (the venous pressure presumably remaining unchanged) This is seen if the line connecting pre- and post diamox values in Fig 15 is extended to its point of section with the abscissa axis (i e the venous pressure) But in some of the cases this would give a venous pressure far outside

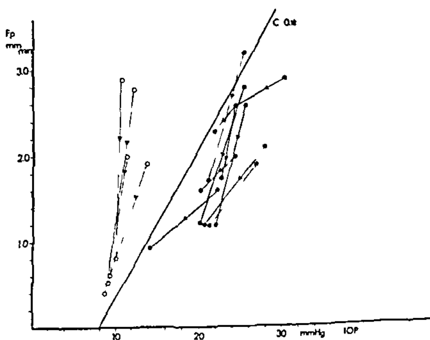


Fig 15
Diamox® intravenous inj (O) and administration perorally (●) Before and after observations connected

some cases in others there are transitory effects but probably without resistance change So far in 20 cases of glaucoma and glaucoma suspects no significantly increased resistance has been found

We are dealing here with an impulse function (approximately) in the water administration This causes a response in the flow of aqueous which depends on a series of factors outside the eye such as buffering osmotic pressure regulations the efficiency of which certainly differs from one person to another A flow effect is provoked which is no longer an impulse function The pressure effect is secondary and its shape may be influenced by local factors Since the flow effect is so different individually one may object that the water provocation test ays little about the ability of the eye to tackle flow fluctuations On the other hand perhaps it is of greater interest to learn how dietary provocations of a kind closely related to those of daily life affect the eye pressure than a standard flow impact to the eye With that point of view the provocation test as generally performed seems in order

I have now come to the end of this somewhat patchy survey of evidences in favour of an ocular pressure regulation Some elementary ideas from a technological branch have been presented with the hope that they could be of some help when hypothetizing about ocular pressure problems

No doubt all this interest in regulation of the intraocular pressure is secondary to our interest in the glaucoma disease Regretably we have to admit that very little is as yet known about the former concerning the latter glaucoma, hardly more is known today than was known when Bjerrum first traced the arcuate scotomas with a piece of paper against his consulting room door (36)

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outflow resistance to decrease in order to compensate for the increased flow with a regulation of pressure in consequence

A series of experiments by Wiebert (35) clearly show that the pupillary flow is increased after water administration There are however considerable differences in the flow response (Fig 17) A resistance decrease seems to occur in

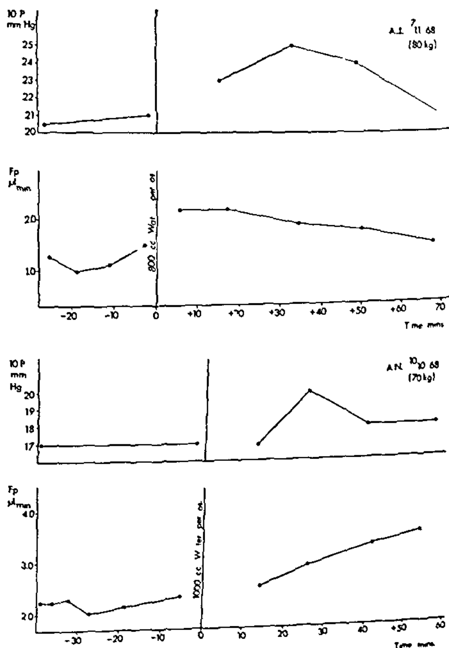


Fig 17
Water provocation tests (Wiebert)

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LIGHT SCATTERING IN LENSES WITH EXPERIMENTAL CATARACT

BY

BO PHILIPSON

Introduction

Transparency of the normal lens and loss of transparency in the cataractous lens are both incompletely understood The physical basis for transparency of the normal lens was thoroughly studied by *Trokel* (1962) He concluded that the small reduction in intensity of visible light passing through the lens was due mainly to scattering and the high transmittance was derived from the high spacial order of the lens fibers and the almost paracrystalline state of the lens proteins The quantitative distribution of proteins was determined in normal rat lenses (*Philipson* 1969A) and in lenses with experimental cataract (*Philipson* 1969B and 1969C) The microradiographically determined protein concentration was shown to be correlated with the refractive index found in various regions of the lens It was assumed that the major loss of transparency in the cataractous lenses was caused by light scattering in the steep protein gradients frequently observed Consequently the protein concentration is of great importance to transparency and to other optical properties of the lens Very little is known about the interaction of light with the nontransparent lens substance in cataractous lenses The aim of the present investigation was to study this interaction in lenses with X ray and galactose cataract

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Material and Methods

Material The experimental procedure concerning animals male Sprague Dawley rats and microradiography was the same as that employed in previous studies (*Philipson* 1969A 1969B and 1969C) Thus only the outlines of the procedure will be given One group of rats were fed on a normal diet and the eyes were examined ophthalmoscopically to exclude lenses with opacities The control lenses and the cataract lenses were always taken from animals of the same age A second group of rats 20 days old were fed on mixed diet consisting of 40 per cent of anhydrous D Galactose and 60 per cent ground chow during 28 days After this period the rats were fed only normal diet during 9 months A third group of rats 10 days of age were exposed on the right eye to 1000r copper filtered X rays generated at 185 kV from a tungsten anode The rest of the animal was protected by a lead shield the left lens being used as control

The *quantitative microradiographic procedure* involves freeze sectioning of frozen lenses to a thickness of about 10 μm freeze drying of the sections and exposure to soft X rays (3 kV) together with a reference system The microradiographs were densitometrically evaluated in order to obtain the dry mass of different regions The dry mass was expressed as mass per unit volume of protein thus including in the order of 5 per cent nonprotein constituents A detailed description of this technique has been presented elsewhere (*Lindstrom & Philipson* 1969 *Philipson & Lindstrom* 1969)

The *transmission of visible light* in freeze sectioned lens sections 10 μm thick was determined after the specimen had been mounted in glycerol between quartz glasses The measuring field was 10 μm in diameter and the wavelength region from 400 nm to 800 nm was scanned in a microspectrophotometer (Zeiss UMSP I) This is a dual beam recording instrument and quartz glasses containing only glycerol were used as reference

Measurements of light scattering were performed with the following equipment a low power helium neon gas laser (Spectra Physics 130) a circular film

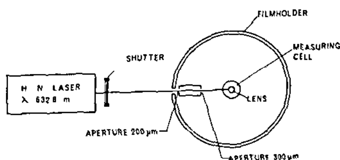


Fig 1
The equipment for light scattering measurements

holder 146 mm in diameter a collimator system consisting of two pinhole apertures with diameters of 200 μm and 300 μm situated 39 mm apart to reduce diffraction from the apertures and a circular measuring cell with Ringer solution (Fig 1) The collimated laser beam (λ = 632 8 nm) contained the essential intensity of light within a diameter of 0 3 mm in the center of the measuring cell where the lenses were placed Scattered light was recorded on a panchromatic emulsion (Panatomic X film Kodak) for which the density is a linear function of the logarithm of the exposure time for densities from about 0 2 up to about 1 5 Each film was evaluated twice in a densitometer (Zeiss Schnell photometer II) with a measuring field of 0 3 by 4 mm the long axis of the slit being parallel to the axis of the film holder Due to the large measuring field a mean scattering level was obtained and thereby the effect of interference patterns in the film from the coherent laser light was smoothed out

Results

Galactose cataract

The development of galactose cataract has previously been studiet by quantitative microradiography (*Philipson* 1969C) but this investigation comprised only rats fed a high galactose diet for 28 days or less In the last stage the whole lens was then very cloudy and the center was totally nontransparent

In the present investigation rats were fed a normal diet during nine months after the initial 28 days of galactose feeding During this subsequent period the cortex of the lenses cleared up and became highly transparent At the end of the experimental period the lenses characteristically had three separate regions each with different transparency (Fig 2) The central region comprised a nuclear cataract, which was completely opaque on slit lamp examination (Fig 3) Peripheral to this region there was an opalescent intermediate zone with small discrete opacities The major part of the cortex was almost as transparent as the cortex in control lenses and the small opacities were usually observed in the peripheral part of the cortex

Microradiographs were registered from freeze dried central lens sections (Fig 4) The major part of the cortex revealed an almost normal arrangement of lens fibers and a homogeneous distribution of protein In the peripheral cortex minor regions were recognized with irregularly shaped lens fibers The intermediate zone of the lens contained larger regions with disarranged and irregularly shaped lens fibers with a varying protein content (Figs 4 5) The central part of the nucleus corresponding to the opaque region showed microradiographically an irregular appearance conspicuously differing from the very homogeneous distribution of protein in normal lenses The major part of the central nucleus had a high protein concentration but regions of varying

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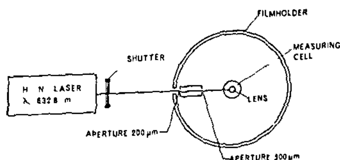


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Material and Methods

Material The experimental procedure concerning animals male Sprague Dawley rats and microradiography was the same as that employed in previous studies (*Philipson* 1969A 1969B and 1969C) Thus only the outlines of the procedure will be given One group of rats were fed on a normal diet and the eyes were examined ophthalmoscopically to exclude lenses with opacities The *control* lenses and the cataract lenses were always taken from animals of the same age A second group of rats 20 days old were fed on mixed diet consisting of 40 per cent of anhydrous D Galactose and 60 per cent ground chow during 28 days After this period the rats were fed only normal diet during 9 months A third group of rats 10 days of age were exposed on the right eye to 1000r copper filtered X rays generated at 185 kV from a tungsten anode The rest of the animal was protected by a lead shield the left lens being used as control

The *quantitative microradiographic procedure* involves freeze sectioning of frozen lenses to a thickness of about 10 μm freeze drying of the sections and exposure to soft X-rays (3 kV) together with a reference system The microradiographs were densitometrically evaluated in order to obtain the dry mass of different regions The dry mass was expressed as mass per unit volume of protein thus including in the order of 5 per cent nonprotein constituents A detailed description of this technique has been presented elsewhere (*Lindstrom* & *Philipson* 1969 *Philipson* & *Lindstrom* 1969)

The *transmission of visible light* in freeze sectioned lens sections 10 μm thick was determined after the specimen had been mounted in glycerol between quartz glasses The measuring field was 10 μm in diameter and the wavelength region from 400 nm to 800 nm was scanned in a microspectrophotometer (Zeiss UMSP I) This is a dual beam recording instrument and quartz glasses containing only glycerol were used as reference

Measurements of light scattering were performed with the following equipment a low power helium neon gas laser (Spectra Physics 130) a circular film

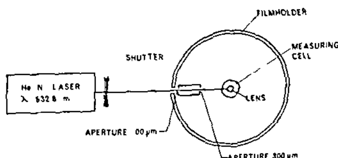


Fig 1
The equipment for light scattering measurements



Fig. 4

Microradiograph from a central section about 10 μm thick of a lens with galactose cataract taken from the same rat as in Fig ? The light areas correspond to a high concentration of protein The inhomogeneous distribution of protein is conspicuous in the central region of the lens Artifact fractures in the freeze dried sections are present The main part of the capsule was lost a minor part being transposed over the section to the left Magnification 50 ×

Fig 5

Microradiograph from a central section about 10 μm thick of a lens with galactose cataract taken from the same rat as shown in Fig 2 Only the inner part of the cortex and the outer part of the nucleus are shown To the left the homogeneous distribution of protein in the cortex In the intermediate zone distorted lens fibers with minor variations in protein content A thin artifact fracture partly divides the latter zone from the central part of the nucleus to the right Magnification 100 ×



Fig 2
Microphotograph of a lens with galactose cataract 9 months after galactose feeding The opaque nuclear cataract the opalescent intermediate zone and the highly transparent cortex are recognized Magnification 20 ×



Fig 3
Slit lamp microphotograph of the same lens as in Fig 2 A thin pencil of light was directed from the right on to the opaque nucleus The reflection in the lens capsule can be observed The incident beam interacted with a small part of the central region and the whole region became bright because of multiple light scattering Magnification 20 ×

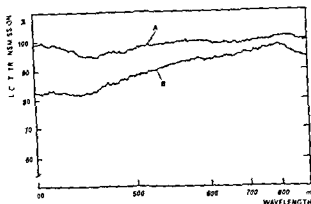


Fig 7

Transmission of light as function of wavelength from a lens section about 10 μm thick adjacent to that shown in Fig 4 Scan A was registered in the middle part of the cortex and scan B in the central part of the section The me suring field was 10 μm in diameter

with galactose cataract The intensity of scattered light measured as photographic density was plotted in diagrams as function of the deviation from the direction of the deviation from the direction of the incident beam Mean values of the photographic density at different angles are given in Table I for three lenses and two representative curves are shown in Fig 8 The scattered

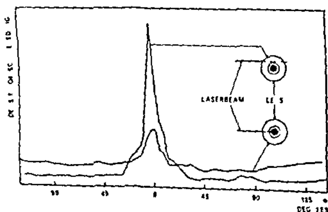


Fig 8

Angular distribution of scattered light as measured by the photographic density from two regions with different transparency in the lens with galactose cataract shown in Fig ^

size with low protein concentration were numerous (Figs 4 5) The protein concentration expressed in g cm⁻³, was plotted as function of the distance from the center of the lens A representative diagram of the protein concentration in these lenses is given in Fig 6 which also includes a diagram for a control lens of the same age Both lenses had about the same concentration of protein in the cortex The major part of the opaque nucleus had a very high protein concentration which amounted to about 1 1 g cm⁻³ Within and at the outer border of this nuclear region the protein distribution showed steep gradients generally with a magnitude of about 0 2 g cm⁻³ over a few micrometers Some gradients reached a magnitude of about 0 5 g cm⁻³ over a few micrometers

Microspectrophotometric measurements were performed on central sections adjacent to those microradiographed The transmission of light was determined as function of the wavelength from 400 nm to 800 nm in five lens sections from each of two cataractous lenses In each specimen scans were taken *in the cortex* in the peripheral nucleus and in the central region of the nucleus Two representative records are presented in Fig 7 In all scans registered the transmission decreased continuously from 800 nm towards shorter wavelengths (~ 450 nm) This reduction was always more prominent in the central nucleus the decrease ranging from 10 to 20 per cent In all other regions this increase in transmission was less than 10 per cent No absorption peaks could be recognized in any of the scans

Light scattering measurements were performed by directing the thin laser beam through each of the three regions with different transparency in lenses

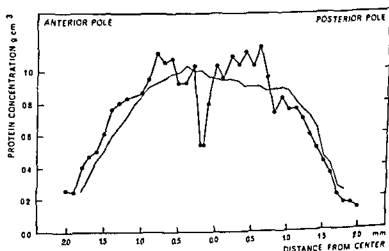


Fig 6

Galactose cataract Distribution of protein along the optic axis in the lens section shown in Fig 4 (thick line with filled circles) and *in a control* lens of the same age (thin line)

light from a particular region had about the same angular distribution for all lenses The spacial distribution of scattered light from the inner part of the transparent cortex in cataractous lenses was practically the same as that of control lenses (Tables I II) Scattered light from the opalescent zone showed an angular distribution similar to that for the cortical scattering However the magnitude of back scattered light here given as the ratio between the photographic density at 135 degrees and the density at 45 degrees was reduced (Table I) When the incident beam was directed towards the center of the opaque nucleus the corresponding ratio was increased and the intensity of the transmitted laser radiation was very weak

X-ray cataract

The development of X ray cataract has earlier been studied biomicroscopically and microradiographically (*Philipson* 1969B) The peripheral cortex 0 3 mm thick was relatively transparent but the remaining regions of the lens were opaque and greyish However these opaque regions were more transparent and not as intensly white in appearance as nuclear galactose cataracts The most prominent feature in X ray cataracts was a membranous opacity in the peripheral cortex corresponding to a steep and sharp protein gradient of about 0 2 g cm³ within a few micrometers as determined microradiographically Inside this interface the structure of the cortex was distorted and irregular

When the peripheral transparent zone in intact cataractous lenses was illuminated by a thin slit shaped beam of light a conspicuous observation was made A large portion of the light followed the peripheral cortical zone around the lens and caused a relatively strong marginal glow on the opposite side of the lens (Fig 9)

Microspectrophotometric measurements of the transmission of visible light were performed on *central* sections from control lenses and from lenses with X ray cataract No absorption peaks were observed in the wavelength scans from any region in the lens sections However the transmission decreased about 10 per cent from 800 nm to 400 *nm* and the scans were very similar to those from galactose cataracts This decrease was a few per cent higher in regions with distorted lens fibers

Light scattering was determined from two normal lenses and three lenses with mature X ray cataract The thin laser beam was directed through two different regions of the lenses In one case the beam passed through the almost transparent peripheral cortex and touched the membranous opacity in the cataractous lenses In the other case the beam passed through the center of the lenses The amount of scattered light was determined in much the same way as for lenses with galactose cataract Somewhat varying exposure times were used but the photographic density caused by scattered light at the angles 45

Table I

Galactose cataract Intensity of scattered light at different angles given as mean values of the photographic density

Lens region	Photographic density (D)				Back scattering ratio
	Deviation angle				
	0°	45°	135°	−45°	D_{135}/D_{45}
Transparent inner cortex	1 90	0 41	0 36	0 42	0 97
	1 90	0 27	0 26	0 30	0 96
	1 85	0 12	0 11	0 14	0 92
Opalescent outer nucleus	1 85	0 36	0 22	0 35	0 61
	1 70	0 32	0 20	0 45	0 63
	1 65	0 35	0 22	0 44	0 63
Opaque central nucleus	1 00	0 70	0 85	0 50	1 36
	0 65	0 22	0 31	0 26	1 41
	0 70	0 28	0 37	0 28	1 32

Table II

X ray cataract and controls Ratio of back scattered light to forward scattered light and ratio of forward scattered light at two different angles Light intensity calculated from the photographic density

Lens region		Ratio of photographic densities (D) at different angles	
		D_{135}/D_{45}	D_{-45}/D_{45}
Normal lenses	Peripheral cortex	0 86	1 00
		0 86	1 00
	Central region	0 79	1 00
		0 90	1 00
X ray cataract	Peripheral cortex	1 02	1 00
		1 25	0 79
		1 00	0 88
	Central region	0 96	0 96
		1 00	1 00
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	1 90	0 27	0 26	0 30	0 96
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	1 70	0 32	0 20	0 45	0 63
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Fig 9
Slit lamp microphotograph A slit shaped beam of light was directed towards the right peripheral cortex Notice marginal glow to the left Magnification 18 ×

135 and − 45 degrees was always less than 0 8 The ratios between photo graphis densities at different scattering angles are given in Table II

Discussion

The optical properties of the three different zones in lenses with *galactose cata ract* might to a great extent be explained by the distorted structure and the local variations in protein concentration as revealed by microradiography It has been shown that protein concentration microradiographically determined can be transformed to refractive index by utilizing the Gladstone Dale formula (*Barer & Joseph* 1954 *Philipson* 1969A) The numerous irregular protein gra dients observed in the central opaque region generally had a magnitude of about 0 2 g cm^{-3} corresponding to a difference in refractive index of about 0 036 An interaction with more than twenty interfaces between different levels of protein concentration occured within the opaque region when a ray of light passed through the center of the lens (Fig 4) Incident light thus stroke the interfaces at different angles and light quanta were then scattered and re fracted in each of these interfaces The intensity of reflected light is mainly dependent on the refractive indices and the angle of incidence at each inter face (*Jenkins & White* 1957 *Strobel* 1960) Because of the irregular shape of the interfaces and the calculated differences in refractive index it could be assumed that a very small fraction of incident light will pass the center of these cataractous lenses without being reflected at least once

The determinations of the transmission of light at different wavelengths did not give any indications that resonance absorption was present within the visible spectrum in any of the lenses investigated The small decrease in trans mission of light towards short wavelengths might be explained by the fact that scattering of light increases with some power of the frequency

In lenses with galactose cataract the forward scattering of light was stronger than the back scattering in both the transparent cortex and in the opalescent zone The principal light scattering processes depend on the dimensions of the scattering sources (*Stacey* 1956) The structures which might cause scattering in these regions were mainly situated in distorted lens fibers and had dimen sions on the order of a wavelength of light Such structures show a prepon derance of forward scattering which was found in these two zones

The strong back scattering of light from the opaque center of the cataractous lenses might be explained as scattering from large structures with dimensions several times the wavelength of light Reflection which is caused by construc tive interference of scattered light from large particles such as interfaces be tween regions with different protein concentrations was probably most promi nent in the opaque regions The major part of nonreflected light was further more refracted in these interfaces The back scattering was favoured because of the great number of interactions and the strong attenuation of the incident beam in the forward direction Furthermore scattering from disarranged pro tein molecules and from groups of large protein molecules contributed to the total scattering from the nucleus The magnitude of this scattering could not be determined with the present equipment However the center of the lens in earlier stages of cataract was transparent as long as the distributed protein was uniform and without any steep protein gradients (*Philipson* 1969C) Consequ ently scattering from small particles will probably comprise only a minor por tion of the total scattering from this region of the lens

In mature X ray *cataractous lenses* the marginal glow observed on illumina tion of the peripheral cortex (Fig 9) might be explained by total and partial reflections in the inner surface of the lens capsule and in the interface towards the opaque region of the lens This interface corresponded to a gradient be tween the different protein concentrations in the peripheral cortex and the inner opaque region of the cortex The peripheral almost transparent zone of the cortex thus functioned in a way similar to fiber optics

Scattered light from the control lenses showed a comparatively high forward scattering in both the peripheral cortex and in the central region of the lens In the X ray cataractous lenses the back scattering from the peripheral cortex was higher than that from the controls An asymmetric forward scattering was found in two of the three lenses These results might be explained by reflection of a fraction of light in the interface situated about 0 3 mm inside the capsule in the cataractous lenses

The almost equal magnitudes of the forward scattering and the back scattering, when the laser beam was directed towards the center of the lens was probably caused by a combination of different kinds of light interaction Both reflection from large interfaces and scattering from regions in distorted lens fibers contributed to the total intensity of scattered radiation in different directions which might explain the intensity distribution obtained The loss of transparency in cataractous lenses is mainly caused by complex scattering phenomena in which many different structures will be involved The main scattering sources are gradients in refractive index between different regions These gradients form interfaces between different protein concentrations such as those revealed by microradiography, but are also present in distorted lens fibers and disarranged protein molecules Since scattering sources of varying sizes are present in cataractous lenses the different scattering processes interfere with each other Thus the given interpretations of light scattering measurements are simplifications of the real nature of the interactions of light with the cataractous lenses

Summary

Experimental cataracts in rat lenses were induced in one group by feeding the animals a high galactose diet and in another group by exposure to X rays The galactose cataractous lenses were investigated at a stage in which the lenses characteristically had three regions with different transparency an opaque nuclear region an intermediate opalescent zone and a transparent cortical region The most conspicuous feature was a pronounced variation in protein concentration in the central region as determined by quantitative microradiography Irregular interfaces were formed between region with different protein concentration The transmission of visible light was determined in different areas within thin lens sections The microphotometrically recorded wavelength scans did not reveal resonance absorption in any region of the cataractous lenses Different regions of intact lenses with galactose cataract were exposed to a thin collimated laser beam ($\lambda = 633$ nm) and the intensity of scattered light was determined Light interacting with the central opaque region was almost totally scattered The high intensity of back scattered light was interpreted as scattering from the interfaces revealed microradiographically In lenses with mature X ray cataract the angular distribution of scattered light was relatively uniform when the incident light was directed towards the center of the lens This was interpreted as a combined effect of scattering from structures of different sizes

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DEAD DEGENERATE, AND LIVING CELLS IN CONJUNCTIVAL FLUID AND MUCOUS THREAD

BY

M S NORN

The conjunctival fluid and the precorneal film contain cells of which some originate from the blood stream e g neutrophilic leucocytes and some are cells desquamated from the conjunctival and the corneal epithelium

The object of the present study was to throw some light on the questions whether these cells are dead degenerate or quite undamaged living cells and whether the contents of damaged cells will increase in relation to certain clinical states

According to *Simpson* a cell can presumably be characterized as dead the moment the granules in the cytoplasm have lost their motility

Failing phagocytosis and failing pseudopod motions are less certain signs of death The cell may still be alive even if these activities are absent *(Simpson)*

The vital function of the cell may further be assessed by its oxygen consumption enzymic activity absorption of tritium labelled tymidine by its growth in tissue culture and by supravital staining

For supravital staining a cell suspension is mixed with a weak dye dilution Living cells with an intact cell membrane remain unstained whereas degenerate and dead cells become stained

Apparently the various dyes differ in ability to stain damaged cells Thus

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some seem to stain only totally dead cells while others also stain mildly damaged degenerate cells

Holmberg found trypan blue and lissamine green to stain dead cells only while eosin and erythrosin also stain cells damaged relatively little

Fleischmann et al observed that neutral red stains at beginning cell death while trypan blue does not stain till the cell is properly dead having presented the first postmortal structural changes Their investigation comprised leucocytes from blood pus and urine

Hathaway et al studied the vitality of bone marrow cells by tissue culture compared with vital staining with trypan blue acridine orange and eosin They noticed fair agreement between tissue culture rate and trypan blue staining on exposure to heat and cold The best agreement was seen between tissue culture rate and acridine orange staining and the poorest between tissue culture and eosin

Pappenheimer studied the vitality of lymphocytes from the thymus and tonsil of rats by staining with trypan blue The cells were damaged at pH values outside the range of 7 0 8 0 at temperatures above 50° and in response to oxygen deficiency fasting etc

Talstad using Sternheimer & Malbin s method (gentian violet and safranine) studied the supravital staining phenomenon on leucocytes from pus in cases of purulent meningitis from blood and from urine She found the phenomenon to depend not only on the vitality of the cells but also on the number of cells fewer cells being stained at a high cell concentration The staining also depends on the dye concentration (a greater number of cells being stained at a high concentration) and on the time the cells are exposed to the dye (the longer the exposure the more intense is the staining)

Mueller studied the vitality of corneal endothelium by staining with nitro blue tetrazolium in order thereby to evaluate different methods of storing material for corneal transplantation

To my knowledge no investigations are available into the vitality of cells in the conjunctival fluid On the other hand it is a well known fact that cells in the conjunctiva and on the cornea may be degenerate such being in some cases vital stained by rose bengal *for instance*

Preliminary Investigations

Trypan blue was preferred for the present investigation first because this dye causes no irritation on instillation into the conjunctival sac secondly because its

properties as a vital stain for the cornea and conjunctiva have been studied in the slit lamp (*Norn* 1967) and finally because vital staining of a cell by this dye shows that the cell is dead

Examination using *rose bengal* was also carried through because this is a well known vital stain and because being related to eosin it possibly stains both dead and degenerate reversibly damaged cells

60 preparations of smears from the tongue and of conjunctival cells were subjected to preliminary examination

Smears from the Tongue

Smears from the tongue were found to contain numerous partially cornified nucleated squamous cells These cells were subjected to staining after desiccation air-fixation or fixation with formalin or profixx

The results differed somewhat but no significant difference was noticed between fixed and non fixed preparations

Staining with a mixture of trypan blue and rose bengal may give an uncharacteristic mixed colour In such cases the result may be difficult to interpret

Staining first with trypan blue and thereafter rose bengal gives a more characteristic colouring

Staining with 1 % trypan blue gave most of the cells a blue colour indicating that they were dead At lower concentrations fewer cells were stained blue The remainder were still stained sufficiently by rose bengal in a corresponding concentration

The concentration of trypan blue was thus seen to be a critical point in relation to simultaneous staining with rose bengal Trypan blue concentrations exceeding 1 % were useless because the dye is only sparingly soluble in water

Similarly 1 % *merbromin* might predominate over a previously employed trypan blue whereas 0 25 % merbromin did not interfere with the trypan blue staining

Trypan blue 1 % and thereafter merbromin in a concentration of 0 25 % stained the cells blue throughout or the nucleus blue and the cytoplasm yellow

Trypan blue or rose bengal alone stained the cells weakly in a dilution as low as 1 40 of a 1 % solution while a dilution of 1 80 gave a hardly visible colouring

A corresponding staining followed by staining with 0 25 % merbromin gave just recognizable colouring in dilution 1 20

1 % rose bengal stained all the cells when used alone or followed by 0 25 % merbromin

Using 0 25 % merbromin alone the cells assumed a fine yellow colour

Conjunctical Fluid Sucked with Pipette

Of the conjunctival cells sucket with a pipette (see later) a fairly great number became blue after instillation of first 1 % trypan blue and thereafter 1 % rose bengal into the conjunctival sac Vital staining with a mixture (0 5 % of each) on the other hand gave only red cells 0 25 % merbromin alone gave a good representation of the cells

Cells pipetted from the eyes of dead persons were examined after vital staining first with 1 % trypan blue and thereafter with 0 25 % merbromin All the cells were stained blue indicating that they were dead

Mucous Thread in Inferior Conjunctival Fornix

The mucous thread in the conjunctiva (see later) was examined both in a fixed and in a non fixed preparation The former mode of preparation is preferable because in a non fixed preparation the cells may have blurred outlines and the colour may be indistinct Mixed staining may be difficult to interpret 1 % trypan blue was found to be useful whereas ½ % was too weak

Vital staining with 1 % trypan blue and 1 % rose bengal instilled consecutively into the conjunctival sac gave satisfactory colouring of the cells in the mucous thread

In the cases where the mucous thread was not removed from the conjunctival sac till 5 10 minutes later the cells had a very pale colour often with coarse blue grains in the cytoplasm

Conclusion

The preliminary investigations showed that the result of vital staining simultaneously with trypan blue and rose bengal depends on the concentration Carrying through of two experimental series has therefore been preferred one series stained first with 1 % trypan blue and thereafter with 0 25 % merbromin and the other stained first with 1 % rose bengal and thereafter with 0 25 % merbromin

Using the chosen concentrations the cells stained entirely or in part by trypan blue were supposed to be dead while rose bengal stained cells were more or less degenerate Living cells remained unstained until merbromin was subsequently added

Procedure

The material used for the investigation comprised partly cells sucked from the conjunctival fluid and partly the mucous thread in the inferior conjunctival fornix

Conjunctical Fluid

0 01 ml of a 1 % vital stain solution was instilled into the conjunctival sac The patient blinked a few times to distribute the dye solution over the whole con junctiva and cornea The conjunctival fluid was sucked up about 15 seconds later

The fluid was sucked laterally from the inferior conjunctival fornix into a special standardized pipette constructed by the author *(Norn* 1960)

This pipette sucked the volume of conjunctival fluid contained within a π mm^2 area of conjunctival mucosa (just over 3 mm) Suction was performed five times

The fluid became deposited as fine drops on the inside of the pipette

The rubber bulb used for sucking the conjunctival fluid was then removed and 10 % formalin was introduced through a capillary tube Then conjunc tival fluid and fixative were mixed and the mixture was pressed down on a glass slide where it dried up

The instilled vital stain was diluted altogether about 1000 times partly by the conjunctival fluid present (1 1) and partly by fixative (a quarter filled capillary tube corresponds to 100 μl Conjunctival fluid from 15 mm cor responds to 0 1 μl cf *Norn* 1966)

Desiccation was followed by after staining with 0 25 % merbromin for one minute washing in tap water alcohol and xylol and finally embedding

Addition of formalin effected killing of cells and dilution A "snapshot of the vitality of the cells was developed immediately before the addition of for malin

Mucous Thread

Both normals and patients have a cell containing mucous thread situated lengthwise in the inferior conjunctival fornix *(Norn* 1967) This thread is stained distinctly by rose bengal and less so by trypan blue

After vital staining and suction with pipette laterally in the inferior fornix as described above the mucous thread in the inferior fornix was removed be tween two wooden sticks and transferred to a slide where it was fixed with profixx (a rapidly drying spray fixative Skandialab Copenhagen)

The desiccated preparation was subsequently after stained with 0 25 % mer bromin for one minute washed in water alcohol and xylol and finally em bedded

On examination of the mucous thread the vital stain was diluted for about 60 seconds by the tears in the conjunctiva By this time any visible superfluous vital stain had disappeared

Clinical Material

The clinical material examined comprised a total of 200 preparations from 109 eyes of 76 patients Of these 122 had been stained *in vivo* with trypan blue and 78 with rose bengal

The clinical material was composed as illustrated in table 1

Neutrophilic Leucocytes

Both dead degenerate and living cells were represented in the conjunctival fluid and the mucous thread The percentage of each category of cells was found to vary considerably

On an average about one fourth of all the neutrophilic leucocytes were stained blue by trypan blue indicating that these cells were dead In some cells the blue colour was limited to the nucleus while in others it included the cytoplasm

About three fourths of all the cells were stained red by rose bengal indicating that they were either dead or degenerate

Finally one fourth of the cells were stained yellow by merbromin added to the rose bengal stained preparations indicating that these cells were alive and undamaged

Thus about one fourth of the cells were dead about half degenerate and about one fourth alive and undamaged

The cells seemed to have the same degree of vitality whether orginating from conjunctival fluid or from the mucous thread in the inferior conjunctival fornix (table 1 graph I)

Nucleated Squamous Cells

The nucleated squamous cells constituted the largest proportion of the conjunctival epithelial cells in the total material

These cells originated from the surface of the bulbar conjunctiva from the area along the lid margin and from the cornea (*Norn* 1960)

In the material as a whole more than half of the cells were dead while only 8 1/ per cent were alive and the remainder degenerate (table 2)

No significant difference was found between cells from the conjunctival fluid and cells originating from the mucous thread

Dead conjunctival nucleated squamous cells were observed to be more frequent than dead neutrophilic leucocytes

Living and degenerate neutrophilic leucocytes were present in greater numbers than nucleated squamous cells (graph I)

Conjunctical Fluid

0 01 ml of a 1 % vital stain solution was instilled into the conjunctival sac The patient blinked a few times to distribute the dye solution over the whole con junctiva and cornea The conjunctival fluid was sucked up about 15 seconds later

The fluid was sucked laterally from the inferior conjunctival fornix into a special, standardized pipette constructed by the author *(Norn* 1960)

This pipette sucked the volume of conjunctival fluid contained within a 7 mm area of *conjunctival mucosa (just over 3 mm) Suction was performed* five times

The fluid became deposited as fine drops on the inside of the pipette

The rubber bulb used for sucking the conjunctival fluid was then removed and 10 % formalin was introduced through a capillary tube Then conjunc tival fluid and fixative were mixed and the mixture was pressed down on a glass slide where it dried up

The instilled vital stain was diluted altogether about 1000 times partly by the conjunctival fluid present (1 1) and partly by fixative (a quarter filled capillary tube *corresponds to* 100 µl *Conjunctival fluid* from 15 mm cor responds to 0 1 µl cf *Norn* 1966)

Desiccation was followed by after staining with 0 25 % merbromin for one minute washing in tap water alcohol and xylol and finally embedding

Addition of formalin effected killing of cells and dilution A snapshot" of the vitality of the cells was developed immediately before the addition of for malin

Mucous Thread

Both normals and patients have a cell containing mucous thread situated lengthwise in the inferior conjunctival fornix *(Norn* 1967) This thread is *stained distinctly by rose bengal and less so by trypan blue*

After vital staining and suction with pipette laterally in the inferior fornix as described above the mucous thread in the inferior fornix was removed be tween two wooden sticks and transferred to a slide where it was fixed with profixx (a rapidly drying spray fixative Skandialab Copenhagen)

The desiccated preparation was subsequently after stained with 0 25 % mer bromin for one minute washed in water alcohol and xylol and finally em *bedded*

On examination of the mucous thread the vital stain was diluted for about 60 seconds by the tears in the conjunctiva By this time any visible superfluous vital stain had disappeared



Fig 1

Mucous thread Acute infectious conjunctivitis Dead cuboid and squamous nucleated epithelial cells (trypan blue in vivo merbromin in vitro)



Fig 2

Conjunctival fluid sucked up with pipette Infectious conjunctivitis Living neutrophilic leucocytes (trypan blue in vivo merbromin in vitro)



Fig 3

Mucous thread Exophthalmos Degenerated cylindric epithelial cells (Rose bengal in vivo merbromin in vitro)

Table 1

Percentage number of neutrophilic leucocytes alive degenerate or dead in a clinical material comprising 109 eyes 200 preparations vital stained with trypan blue or rose bengal after stained with merbromin *in vitro*
Other represent keratitis corneal erosion exophthalmos instillation of cocaine and silver nitrate

	conjunctival fluid			mucous thread			total of preparations
	alive	degenerate	dead	alive	degenerate	dead	
normal	5	72	23	29	33	38	36
acute inf conj	22	59	19	36	52	12	28
chron inf conj	43	12	45	37	48	15	32
allerg conj	9	62	29	34	27	39	16
blepharoconj	12	63	25	26	45	29	20
chron simple conj	20	68	12	9	68	23	17
keratoconj sicca	22	28	50	3	11	56	12
ectropion	4	71	25	5	33	62	6
other	26	49	2[illegible]	36	34	30	33
average	21	52	27	28	47	25	200



Fig 1

Mucous thread Acute infectious conjunctivitis Dead cuboid and squamous nucleated epithelial cells (trypan blue in vivo merbromin in vitro)

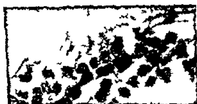


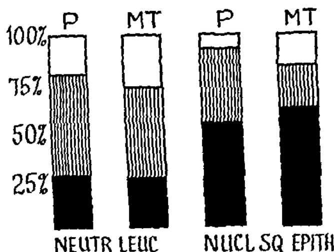
Fig 2

Conjunctival fluid sucked up with pipett Infectious conjunctivitis Living neutrophilic leucocytes (trypan blue in vivo merbromin in vitro)



Fig 3

Mucous thread Exophthalmos Degenerated cylindric epithelial cells (Rose bengal in vivo merbromin in vitro)



Graph I

The percentage distribution of dead (black column) degenerate (hatched column) and living (white column) cells in conjunctival fluid sucked with pipette (P) and in mucous thread (M T) from inferior fornix
Neutrophilic leucocytes (former two columns) and nucleated squamous cells (latter two columns)

Other Cells

The ratio of living to degenerate to dead cells was estimated on the basis of a differential count of as far as possible not less than 100 cells (table 3)

The number of cells was in many cases regrettably small The numbers are shown in table 4

The results of the estimation must therefore be accepted with some reservation

Cuboid conjunctivo epithelial cells More than half of these cells were dead Living undamaged cells were extremely rare.

Cylindric conjunctivo epithelial cells These cells originated from the sur face of the fornices and the tarsal conjunctiva The majority were dead while few were alive and undamaged

The conjunctivo epithelial cells did not differ significantly from each other they were more often dead than the neutrophilic leucocytes

Lymphocytes Only few living lymphocytes were found The number of dead could not be estimated the material being too small (table 3)

Normal Material

The normal material comprised 36 preparations These showed no significant difference from the total material (tables 1 and 2)

Table 2

Percentage number of nucleated squamous cells alive degenerate or dead a total of 136 preparations

	conjunctival fluid			mucous thread		
	alive	degenerate	dead	alive	degenerate	dead
normal	3	38	59	3	26	71
acute inf conj	0	72	28	30	0	70
chron inf conj	0	27	73	20	49	31
allerg conj	17	40	43	32	8	60
blepharoconj	0	36	64	5	19	76
chron simple conj	0	54	46	1	47	52
keratoconj sicca	10	9	81	11	2	87
ectropion	0	23	77	0	14	86
other	25	39	36	38	13	49
average	8	38	54	17	22	61

Table 3

Percentage numbers of living degenerate and dead cells within different cell categories in a total material comprising 200 preparations

	conjunctival fluid			mucous thread			number of preps
	alive	degenerate	dead	alive	degenerate	dead	
neutrophilic leuc	21	52	27	28	47	25	196
nucleated squamous cells	8	38	54	17	2	61	136
cylindric ep cells	25	5	70	10	–	–	25
cuboidal ep cells	0	37	63	1	39	60	28
lymphocytes	3	73	24	5	9	86	15

Table 4

Number of cells within the different cell categories used for differential count with a view to vitality of the cells A total of 200 preparations

number of cells per preparation	< 10	< 25	< 50	< 100	≧ 100	number of preps.
neutrophil leuc.	25	19	25	29	98	196
nucl squam cells	32	30	20	29	25	136
cylindric ep cells	7	3	4	5	6	25
cuboid ep cells	4	2	7	4	8	25
lymphocytes	4	3	2	5	1	15

Pathological Material

In *acute infectious conjunctivitis* there seemed to be a relatively greater number of living neutrophilic leucocytes and a smaller number of dead than normally In *chronic infectious conjunctivitis* the ratio varied

In *keratoconjunctivitis sicca* there were found strikingly many dead neutrophilic leucocytes lymphocytes and epithelial cells both among the cells from the conjunctival fluid and among those of the mucous thread in the inferior fornix

In *ectropion* dead squamous cells cylindric epithelial cells and cuboid epithelial cells were present in a surprisingly great number The ratio of living to dead neutrophilic cells varied

Allergic conjunctivitis blepharoconjunctivitis and *chronic simple conjunctivitis* showed no significant difference from the normal

Varying ratios were seen after instillation of silver nitrate or cocaine. The number of cells was too small to allow of definite conclusions

Discussion

By the procedure described above it was possible to show that the conjunctival fluid and the mucous thread may contain both undamaged living cells degenerate cells and dead cells

It may be objected however that the method is not particularly accurate

Talstad has shown that the time factor plays a certain role. In the pipette preparation the cells were vital stained for about 15 seconds before pronounced dilution took place In the mucous thread preparation the cells were influenced

by a steadily decreasing dye concentration owing to dilution by tears during about one minute

Dilution (about 1000 times) of the vital stain in the pipette sufficed to prevent additional artificial staining The dye was concentrated again however by desiccation on the glass slide

The dilution of the vital stain round the mucous thread in the inferior fornix was possibly insufficient in some cases especially in such with a reduced tear secretion

Despite these sources of error which differed for examination of conjunctival fluid and mucous thread respectively dead and degenerate cells were equally frequent in the two categories of preparations

In many instances the number of cells was to small for reliable differential count a fact which explains at least in part the great difference within the individual clinical group

The mucous thread in the inferior conjunctival fornix acts as a band conveyor which removes foreign bodies and other waste products from the conjunctival fluid and carries them on to the skin at the inner canthus

The mucous thread moves at a much slower rate than the tear flow (*Norn* 1969)

Cells caught by the mucous thread might be conceived to stay so long in the conjunctival sac that they degenerate and die However the number of degenerate and dead cells found in the mucous thread did not exceed that in the conjunctival fluid This goes to show that the mucous thread environment affords optimum conditions for the continued thriving of cells

The neutrophilic leucocytes were more frequently alive than the conjunctivo epithelial cells The latter predominated over the leucocytes among the dead cells

These differences are doubtless in some measure accountable for by a difference in genesis of the cells The neutrophilic leucocytes are cells emigrated from the blood stream being thus often fresh cells drawn chemotactically into the conjunctival fluid

The epithelial cells on the other hand are cells desquamated from the surface epithelium These are often dead or dying cells Quite fresh cells are more rarely shed the binding of the cells being not sufficiently firm.

The many dead cells seen in keratoconjunctivitis sicca may be due to a reduced removal of such via tears and mucous thread (*Norn* 1969)

The dead epithelial cells may also be due to increased degeneration and death in the surface of the conjunctiva and cornea prior to the desquamation as noticed in this disease on vital staining with rose bengal and examination in the slit lamp

In the material as a whole a much greater number of cells were vital stained by rose bengal than by trypan blue This observation bears out the original sup

position that rose bengal stains not only totally dead cells on a line with trypan blue but also degenerate cells, i e stains cells presumably before these have been irreversibly damaged

Summary

The vitality of cells in the conjunctival fluid and on the mucous thread in the inferior conjunctival fornix has been estimated by microscopy after vital staining with trypan blue or rose bengal and after staining with merbromin

Differential counts gave the results that about one fourth of the neutrophilic leucocytes were dead about half degenerate and about one fourth alive and undamaged in a total material of 109 eyes

The conjunctival epithelial cells were relatively more often dead (more than half) and more rarely alive than the neutrophilic leucocytes

The number of dead cells was found to be comparatively large in keratoconjunctivitis sicca and in ectropion

Living neutrophilic leucocytes seemed to be present in relatively large numbers in cases of acute infectious conjunctivitis

No significant difference was found between cells from the conjunctival fluid and cells originating from the mucous thread

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TESTING OF DYSLECTIC CHILDREN BY JAMPOLSKI'S PRISM TEST

BY

M. S. NORN

In 1964 *Jampolski* devised a prism test by which to quickly disclose a possible suppression of one eye.

A prism of four prism dioptres is placed base out in front of one eye. The principle of the method is seen in fig. 1.

The patient is made to look fixedly at a light. A prism placed in front of the right eye of a normal subject will give a double image. The right eye will move so as to become adjusted to the left, which latter will remain unmoved.

The examiner observes the eye that is not covered by the prism. The reaction to Jampolski's test is normal, if the non-covered eye makes no adjusting movement, but is kept quiet or performs rocking movements round the original position (upper half of fig. 1).

Supposing that the left eye is affected with strabismic amblyopia or is suppressed for other reasons, we see the phenomenon illustrated in the lower half of fig. 1.

The right eye will again make an adjusting movement to the left. As, however, *no double image occurs, the left eye will move passively* – like a blind eye – in the same direction as the right, i. e. to the left.

The free left eye is observed as previously, and it is seen to make an adjusting movement to the left of about four prism dioptres. The left eye remains in this position as long as the prism is held in front of the right eye.

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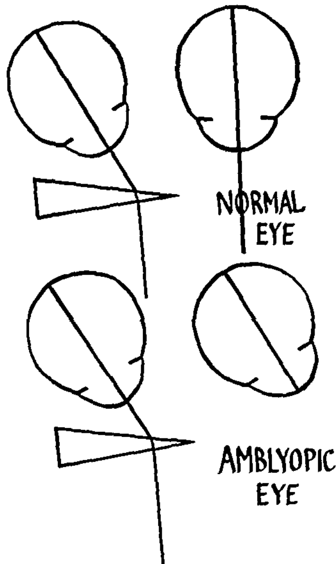


Fig 1
Jampolski s prism test above of a normal eye and below of an amblyopic left eye

By observing the non prism covered eye we attain to the following rule The reaction to Jampolski s test is normal if the non prism covered eye remains un mo ed or makes rocking movements at most when the prism is placed in front of the other eye

The reaction to Jampolski s test is pathological if the non prism covered eye

performs a distinct abducting movement and remains in this new position as long as the prism stays in front of the other eye

Jampolski s test has been employed in Sc Fransisco on a series of dyslectic children *Bettman et al* found the test pathological in 42 per cent out of 47 dyslectic children against only 9 per cent out of 58 non dyslectic

This preponderance of pathological reactions to Jampolski s test among dyslectics is a remarkable observation

Bettman et al themselves interpret their observation as a sign of a certain motor jerkiness of the dyslectic children They state that a similar jerkiness manifests itself by letting the patient follow a pencil passed diagonally before the eye

Gross jerkiness was noticed in 52 per cent of the dyslectic children against 11 per cent of the controls

Jampolski s test is however hardly a test for motor jerkiness but is suitable as a test for suppression as also pointed out by Jampolki himself

An abundant literature is available on ophthalmologic and motor examinations of dyslectics

Norn Rindziunski & Skydsgard recently examined 117 dyslectic children from a suburban school admitting only such children *(Hyldegardsskolen County* of Copenhagen) We concluded from this study that the incidence of eye diseases in the widest sense of this term is not particularly high among proper dyslectics compared with that in a control series

Predominance of pathological reactions to Jampolski s test suggest a particularly frequent occurrence of suppression among dyslectics However we found no such predominance of suppression on comprehensive ophthalmologic and orthoptic examinations

We therefore considered it a matter of interest to study the result of Jampolski s test on a series of proper dyslectics

Present Investigations

Material

The author subjected all the pupils of *Hyldegardsskolen* except a few absentees *to Jampolski s test*

Hyldegardsskolen receives exclusively dyslectic children admitted only after a probation year in the normal school where pupils with retarded reading ability from other causes are sorted out

The series under review may therefore be regarded as one of proper dyslectics with no admixture of other kinds of backward readers

The previous investigation by *Norn Rindziunski & Skydsgard* was based on

pupils from the same school As however it was carried out 5 or 6 years before the present the pupils were different

The present series comprised 84 pupils 63 boys and 21 girls i e a marked predominance of boys as is typical where proper dyslexia is concerned (Table I)

Method

Jampolski s test was employed as described above using a prism of 4 prism dioptres base out The patient fixes a light pencil held at the patient s eye height at a distance of 30 40 cm The test was made several times with the prism in front of the right eye and later with the prism in front of the left Finally the test was repeated while the patient was fixing a cross placed at a distance of 3 metres and a little above the patient s eye height.

The patient was questioned about symptoms during the testing Subsequently the patient was asked direct whether placing of the prism in front of the eye caused double vision

Result

A total of 84 dyslectics were tested Jampolski s test gave normal reactions in all cases exept three One of the latter reacted definitely pathological to repeated testing while the two others displayed varying reactions to repeated tests

Symptoms

The symptoms recorded for 14 of the dyslectic children are seen in Table II

Short term diplopia was recognized by half of the subjects though most often

Table I

Age and sex distribution of 84 dyslectics

Age	9	10	11	12	13	14	>14
boys	5	15	11	12	9	7	4
girls	3	0	7	6	4	1	0
Total	8	15	18	18	13	8	4

Table II
Symptoms of 74 dyslectics during Jampolski s test

	1st symptom	2nd symptom	3rd symptom	Total
diplopia spont recognized	2	9	1	12
diplopia on inquiry	1	15	9	25
image moves	6	14	0	20
sharper image	9	5	0	14
blurred image	2	1	0	3
larger image	20	3	0	23
smaller image	14	1	2	17
larger image smaller contralat	5	1	0	6
varying image sizes	5	0	0	5
unchanged image	10	2	0	12
Total	74	51	12	137

only on direct questioning and on repeated testing Several of the children noticed that the image moved when the prism was placed in front of the eye

A fairly great number observed that the image increased in size or became more distinct while a smaller number saw it to fade or become smaller despite use of a plane prism

The investigation showed that the fusion movement in response to Jampolski s test is a subconscious reaction and that only few immediately recognize the short term diplopia

Case Reports

Only one patient reacted definitely pathologically to Jampolski s test This patient a 10 year old girl displayed a typical pathological reaction of the left eye both for far and for near

Right eye vision 6 6 + 1 0 sph

Left eye vision above 6 18 + 3 5 sph unimproved by cylinder or stenopeic hole Visual acuity the same for far and for near

Sciascopy R L + 1 0 sph L E 4 0 sph

Ophthalmoscopy normal conditions

Orthoptic examination showed suppression of the left eye in response to Worth s 4 light test at a distance of 6 m 4 lights for near

Cover test showed parallel positions for far and latent divergence with rapid re ad justment for near
Accomodation near point 8 6 cm binocularly and of right eye unable to see distinctly with left eye
Fusion reserve 25° for large object 12 13° for detailed object and only 7° for small object
Wirt s stereotest showed full slow stereopsis
Amblyopia treatment and fusion exercises were prescribed in the hope of obtaining better binocular vision.

Two patients showed a doubtfully pathological Jampolski

Boy aged 13
Vision of both eyes 6/6 emmetropia
Convergence near point 1° 16 cm
Fusion reserves were small Synoptophore and Wirt s test gave full and promt stereopsis
Latent divergent strabismus was present for near and for far with quick re adjustment
Treatment for convergence insufficiency was recommended
The reactions to Jampolski s test, being now pathological in the left eye and now normal could not be explained None of the other tests revealed any signs of suppression

A 1? year old boy reacted normally to most Jampolski s tests but on rare occasions pathologically
Mild hypermetropia was noticed on account of which + 1 25 sph was prescribed for either eye for reading
Orthoptic examination showed good fusion reserves Cover test revealed latent convergent strabismus for near and for far with quick re adjustment
There was esophoria of 3 dioptres for near (Maddox wing) and 6 dioptres for far (Madd x rod)
Full and promt stereopsis was noticed
Worth s 4 light test showed 5 lights uncrossed which gathered into 4 for far and 4 lights for near
No signs of suppression were observed

There were thus found three dyslectics with doubtfully or definitely pathological reactions to Jampolski s test All three patients were referred to treatment against their reading handicap Only one child reacted definitely pathologically to Jampolski s test In this case other tests likewise disclosed signs of suppression for which treatment was worth trying

In the two cases with a doubtfully pathological Jampolski other suppression tests afforded no evidence of such It is therefore to be regarded as a matter of chance that these two children were chosen from the series of dyslectics for further testing and treatment.

Discussion

The series under review showed that dyslectics react normally to Jampolski's test The 1 3 per cent pathological cases does not exceed the percentage to be expected in a control series (Cf our control series in *Norn et al s* study)

Bettman et al found preponderance of pathological reactions to Jampolski's test among dyslectic children This discrepancy may be due to misinterpretation of the test if *cases presenting jerkiness are reckoned as pathological In the pre*sent series only unquestionable adjusting movements were regarded as pathological in agreement with Jampolski s statements

The discrepancy may also possibly be due to a difference in selection of the *two series The present must be regarded as a series comprising solely proper* dyslectics

Bettman et al considered the test to be suitable for revealing jerkiness of the eye muscle They noticed a similar jerkiness when the patient followed a pencil passed diagonally before the eye

However, according to *Jampolski* and to the author s own experience the test is taken as an aid to disclose suppression The reaction is pathological in cases of strabismic amblyopia and other forms of amblyopia (e g in central retinal degeneration)

The incidence of suppression was not found to be higher among our dyslectic children than among normals We may therefore conclude on the basis of Jampolski s test on 84 dyslectics that suppression does not predominate among such children

This conclusion harmonizes with our previous conclusions *(Norn Rindziunski & Skydsgard)* to the effect that dyslectics are not more frequently affected with eye diseases than non dyslectics

Such eye muscle jerkiness as *Bettman et al* claimed to have noticed in dyslectic children was not detectable in the present series using a simple test where the patient followed a pencil passed diagonally or as circumduction before the eye

In the present series there were found four with jerky diagonal movement and five with jerky circumduction movement (Three presented both)

Summary

Out of 84 dyslectic children subjected to Jampolski s prism test 1 per cent reacted pathologically while 2 per cent showed uncertain varying reaction Diagonal and circumduction movements rarely revealed jerkiness

The conclusion has been drawn that the incidence of suppression or jerkiness

is not higher among dyslectic children than that to be expected among non dyslectics

Acknowledgement

My thanks are due to Mrs *Else Hammerberg* orthoptist for her orthoptic examinations Further I wish to thank Mr *H Schou Andersen* principal of *Hyldegårdsskolen* for kind assistance in the examinations and the *Education Committee Municipality of Gentofte* for permission to examine the pupils

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STUDIES ON THE THERAPEUTICAL PROBLEM OF UVEITIS

BY

Jiri Velicky

A great advance has been made in the treatment of endogenous uveitis during the last 20 years. Some forms of uveitis settle down fairly readily if corticosteroids, phenylbutasone derivates, antibiotics and protein shock therapy are used at the proper time and if the treatment is adequate to the conditions of the disease. It seems, however, that the present therapy does not influence the tendency of some uveal inflammations to proceed in a chronic and recurrent fashion. Miklos, for example, using the classical therapy, found in the year 1940 the tendency to recurrences in 43.6 % of patients suffering from iridocyclitis. Oksala & Varonen[3] in the year 1966, using the modern therapy, observed also 43 % of recurrences in iridocyclitis. As a matter of fact it is very difficult to obtain even a very approximative information on contemporary results in the treatment of uveitis. The following observations regarding the incidence of recurrent uveitis among the patients admitted to ward in the eye clinics and departments may illustrate to some degree the present state. It is hoped that the methods of investigation employed will be useful to others interested in this problem.

Table I demonstrates some interesting facts gained by a field investigation among czechoslovac university clinics and eye departments of hospitals. Among the patients hospitalised in the year 1955 (total 48 688 of patients) the rate of uveitis amounted to 6.8 %. Among them there were 73.2 % of early recent cases of uveitis and 26.8 % of recurrent and chronic cases. Eleven years later

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Table 1

Ratio between fresh and recurrent cases of uveitis admitted to hospital in 1955 and 1965

	1955	1965
Uveitis	3387 = 100 0 %	2804 = 100 0 %
a/ fresh	2484 = 73.3 %	1701 = 60 7 %
b/ recurrent	903 = 26 7 %	1103 = 39 3 %
Ratio a b	2 77 1	1 5 1

in 1965 the field investigation has been repeated in the same manner The rate of uveitis among 43 103 patients admitted to eye clinics and departments was very similar (6 5 %) The ratio between recent and recurrent cases of uveitis however changed distinctly there were 60 7 % recent cases and the number of recurrent cases increased to 39 3 % The tables No 2 and 3 show the same numbers divided into iridocyclitis and chorioretinitis the ratio is very similar both in anterior and posterior uveitis If the trend towards increasing numbers of recurrent cases admitted to hospital should continue the number of recent and recurrent cases in a few next years would be equal

The management of uveitis has changed considerably since 1955 The question may be asked wheather these changes in the style of management are not responsible for the increasing numbers of recurrent cases or wheather the modern therapy is suitable for the treatment of cases with the tendency to proceed in a recurrent or chronic manner

Table 2

The same table for iridocyclitis only

	1955	1965
Iridocyclitis	[illegible]9 = 100 0 %	2075 = 100 0 %
a fresh	1892 = 73 9 %	1282 = 61 8 %
b recurrent	667 = 26 1 %	793 = 38 2 %
Ratio a b	[illegible]8 1	1 6 1

Table 3

The same table for chorioretinitis only

	1955	1965
Chorioretinitis	825 = 100 0 %	729 = 100 0 %
a/ fresh	529 = 71 5 %	419 = 57 5 %
b/ recurrent	236 = 28 5 %	310 = 42 5 %
Ratio a b	2 5 1	1 5 1

The evaluation of therapeutic effects in recurrent and chronic uveitis is I confess a very difficult business open to all criticism But in spite of all difficulties I will show a table illustrating the effect of treatment of chronic and recurrent uveitis at different periods gained in an alpine sanatorium (Novy Smokovec High Tatra Czechoslovakia) The criterion was the change of the clinical condition of the eye as revealed by biomikroscopic ophthalmoscopic and subjective examinations Mostly cases refractory to the routine treatment were accepted

The 15 years of existence of the sanatorium can be divided into three periods In the years 1951-53 the equipment of the sanatorium was very poor and the treatment was tantamount to pure climatotherapy in an alpine climate supported by such methods as for example atropine mild protein shock therapy vitamins etc In the second period in the years 1954 to 1960 the equipment of the sanatorium was improved to the level of that of an standard eye department treatment with corticosteroids and antibiotics was introduced but in a limited form The methods of treatment followed the conception of A C Woods[5] In the third period up to 1966 the equipment of the sanatorium fulfils all contemporary requirements Some special diagnostic and therapeutic measures have been introduced The style of management is more prone to therapeutical trial and consists more often from therapeutical coctails

It may be seen (table No 4) how intensively the rate of ammeliorations of clinical findings changed respectively to the three periods At the same I must admit our choice of patients suitable for treatment has improved so that all progress cannot be attributed to treatment only In comparison it may also be seen that the result in Eales disease did not change at the same time This suggests that the contemporary progress of pharmacology presents an opportunity to develop more efficient forms of treatment in chronic and recurrent uveitis but the effort of doctors is not always aimed at making the fullest use of these opportunities The question wheather the quick and easy manage

Table 4

Improvement of clinical findings respectively to the three periods

Cases	Disease	Rate of ammeliorations			Difference
		1951–53	1954–60	1961–66	
753	Chorioretinitis	45 %	57 %	64 %	+ 18 %
586	Iridocyclitis	43 %	56 %	63 %	+ 20 %
976	Eales disease	43 %	49 %	46 %	+ 3 %

ment of uveitis by corticosteroids contributes to the development of recurrent or chronic forms of uveitis remains however open

Secondly it is not unreasonable to assume that the treatment of general and local infections by antibiotics chemotherapy and corticosteroids produced by practitioners very often in an inadequate manner contributes to the benign but prolonged course of a variety of infections which are related to the origin of uveitis (Klima[1]) The atypical course of such low grade infections under different immunobiological conditions may also be the source of increasing problems in uveitis

However that may be ophthalmologists are responsible if not for the consequences then for the adequate treatment It is necessary to draw attention to the fact that in a not too far future we shall be busy with the *treatment of recurrent* chronic and dissatisfied patients Untill now there has been tendency to underestimate the dangers of recurrent uveitis and to treat every recurrence by the same methods and means as fresh *recent cases* As a matter of fact the treatment of recurrent uveitis has its own problems arising from the prolonged course and from different secondary *complications caused by the* increase of permeability metabolic disturbances and trophic damages and consequently adequate methods of treatment should be developed (Velicky[4])

Summary

The ratio of recurrent and chronic cases of uveitis admitted to hospital has increased distinctly in the past eleven years It would be advisable to aim the research and effort at developping new and more efficient style of treatment both for recent and recurrent cases of uveitis

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ANOTHER CASE WITH RECURRENT GLAUCOMATOCYCLITIC CRISIS AND ANOMALIES IN CHAMBER ANGLE OBSERVED DURING AND BETWEEN HYPERTENSIVE EPISODES CONTRIBUTION TO ETIOLOGY

BY

PETAR SOKOLIC M D

Etiopathogenetic nature of glaucomatocyclitic crisis is not clear and several opinions have been put forward *Kraupa* (1935) considered it due to vasoneurosis of the ciliary body on allergic basis According to Possner the disease might be caused by certain virus According to Merte and Curschmann the neurovegetative disturbance might play some causative role in the disease Not all the cases however published in the literature had been gonioscopically and tonographically illustrated Among the others this might be one reason for the divergence in opinion about the nature of this enigmatic type of glaucoma Moreover the concept and symptomatology of developmental glaucoma had been put forward by Gorin as late as in 1964 and only a part of cases could have been observed from this aspect

In 1948 Possner and Schlossmann delineated syndrome of recurrent glaucomatocyclitic crisis which has the following characteristics

1 Condition is unilateral
2 The eye is white or slightly congested during the attack
3 Subjective symptoms are minimal and visus is not impaired
4 Signs of cyclitis do not precede the glaucoma and posterior synechiae are not formed
5 Attacks may last from a few hours to a month but rarely more than 2 weeks
6 Between attacks the eye shows no signs of glaucoma or cyclitis

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7 Treatment with *Pilocarpin or Atropin does not shorten the attack*

To our experience there remains to complete this criterio with gonioscopical findings which seem to be characteristic in the eyes with recurrent glaucomato cyclitic crisis

In my paper (Acta Ophthalm (Kbh) *Vol 44* 1966) a male aged 42 with bilateral angle anomalies and *recurrent glautomatocyclitic crisis in the right eye* had been dsecribed The abnormalities in the chamber angles had been of the type seen in the developmental glaucoma *(Gorin* 1964) The uninvolved left eye had moderately raised intraoculare pressure of glaucoma simplex type and anomalies in chamber angle resembling the insertio iridis anterior In the right glaucomatocyclitic eye the ciliary body was covered with a rough sheet of greyish white tissue spread over the posterior trabecular border in an irregular line Glaucoma of the left eye had been considered as developmental glaucoma of usual type whereas recurrent glaucomatocyclitic crisis in the right eye as particular manifestation of developmental glaucoma

Hart & Weatherill (1968) have supported this conception with 7 cases suffering from recurrent glaucomatocyclitic crisis and showing developmental anomalies in the filtration angle According to the opinion of these authors glaucomatocyclitic critis should be considered as one of the developmental glaucomas although retaining its peculiar individuality in view of its clinical manifestation and benign prognosis

The case to be demonstrated is this paper supports furthermore the conception that glaucomatocyclitic crisis is in the essence a particular form of developmental glaucoma

Case report

A clerk aged 55 has been in the treatment for neurovegetative disturbances of heart and gastrointestinal tract for many years Moreover he suffered from scotoma scintilans occuring at irregular intervals The first attack of *recurrent glaucomatocyclitic* crisis occured 4 years ago and started with scotoma scintilans which disappeared after a few minutes whereas intraoculare hypertension associated with slight congestion lasted 3 4 days The following attacks were not initiated with scotoma scintilans His eye disease was not recognized at the beginning So far he remembered there had been 4 attacks of unequal intensity The most intensive was that one in 1967

The patient presented himself for examination in 1967 during the normotensive interval Examination had given the following result

Right external examination revealed slightly pronounced anisochromia iridis the right iris being lighter in colour

Gonioscopy in the optical section by means of narrowed beam of light the angle assumed the shape of a wide and deep U Schwalbes line was displaced anteriorly so that the trabeculum looked abnormaly wide Schwalbes zone was thickened Len

pheral edge of the cornea was rounded Scleral spur was not distinguishable In the posterior half of trabeculum a middly pigmented band could be seen As visible from the Fig 1 transparent fibers as well as iris processes with the structure of iris tissue of various density adhered in irregular intervals to the pigmented band on the tra becular The insertion line of the iris root was irregular On many places the stro mal adhesions did not permit the view into the posterior part of the angle

The other parts of the right eye including the eyeback ground were normal

Visus $-3\,0$ Dsf = 5/5

Tonography

Right Po = 18 mm Hg C = 0 03 cmm min mm Hg
F = 1 84 cmm min

Left Po = 14 mm Hg C = 0 22 cmm min mm Hg
F = 0 88 cmm min

Left analogous anomalies but less pronounced could be seen in the left chamber angle In contradistinction to the right eye the trabeculum in the left eye was not en larged Schwalbe s line was less prominent and more sharply demarcated Peripheral edge of the cornea was wedge shaped

Visus $-3\,^{0}5$ Dsf = 5/5

Examination of visual field of both of eyes did not reveal any defect

On the 7 XII 1968 the patient got the acute hypertensive attack on the right eye associated with headache On the same day he instiled 2 % solution of Pilocarpin into the right eye several times and presented himself for the examination on the next day with the following result



Fig 1

Goni scopic appearance of the angle of the right affected eye The Schwalbe s line is thickened and displaced anteriorly Trabeculum is abnormaly wide Insertion line of the iris is irregular Scleral spur is not distinguishable The angle is bridged by transparent fibers and many iris processes adhering to the trabeculum

Biomicroscopic examination revealed a few pale keratic precipitates and the slight aqueous flare in the right middly congested eye

Gonioscopy the picture of chamber angle remained as above described No alteration in connexion with the attack could be revealed

Tonography

Right Po = 42 mm Hg

C = 0 06 cmm min mm Hg

F = 1 86 cmm min

Left Po = 21 mm Hg

C = 0 30 cmm min mm Hg

F = 3 30 cmm min

Instillation of 2 % Pilocarpin solution 6 × daily and Antidrazi (Italseber) 100 g divided in 4 dosis per os had been prescribed

The examination had been repeated two days later with following result

Tonography

Right Po = 29 mm Hg

C = 0 13 cmm min mm2Hg

F = 2 27 cmm min

Left Po = 20 mm Hg

C = 0 20 cmm min mm Hg

F = 2 0 cmm min

Eight days after the onset of glaucomatocyclitic crisis the patient had been repeatedly examined with the following result

The signs of congestion had disappeared Keratic precipitates had been partly visible

Gonioscopic picture of chamber angle remained the same

Tonography

Right Po = 20 mm Hg

C = 0 23 cmm min mm Hg

F = 2 30 cmm min

Left Po = 16 mm Hg

C = 0 22 cmm min mm Hg

F = 1 32 cmm min

Discussion

As visible from the case report the anomalies revealed in chamber angle had been of the type established in developmental glaucoma *(Gorin 1964)* Gonioscopic picture remained the same during glaucomatocyclitic crisis Thus the gonioscopy could not give any explanation for the lowered value of the coefficient of outflow (C) during the hypertensive episode

In the first of our published cases the heterochromia iridis had been more pronounced than in the case reported in this paper wherein it is slightly pronounced Heterochromia iridis which is more or less pronounced present in the majority of cases with glaucomatocyclitic crisis is to our opinion simple heterochromia" It should be considered accordingly as a developmental defect

of iris It is not a complicated heterochromia because the heterochromia in cases with glaucomatocyclitic crisis is already present at the time of the first attack which is not preceded by cyclitis From this point of view heterochromia iridis in cases with glaucomatocyclitic crisis designates the eye as developmentally defective one and fits into the common frame with developmental anomalies in chamber angle

As regards the possible factors which precipitate the glaucomatocyclitic attacks in such an developmentally defective eye it may be of importance to remember that our patient has suffered from scotoma scintilans and neurovetative disturbances of heart and gastrointestinal tract His recurrent glaucomatocyclitic attacks may be accordingly considered as particular manifestation of neurovegetative disorder of the developmentally defective iridociliary sector and filtration angle His eye disease fits accordingly into the frame of late developmental glaucoma

The more one is familiarized with the gonioscopical morphology of developmental anomalies of chamber angle the more frequently one encounters glaucomas with the signs of developmental disorders in chamber angle It is logical to bring these anomalies in the causal connexion with glaucoma in the case respected On the other hand gonioscopy is still today too gross a method of examination to detect delicate changes in the trabecular meshwork Thus in the case reported the mechanism of elevation of intraoculare pressure during the hypertensive episode remained to be conjectured

Summary

Report of a case with glaucomatocyclitic crisis observed during and between hypertensive episodes has been presented The case showed anomalies in chamber angle of the type established in developmental glaucoma The case has been discussed as suggestive of the causal connexion between glaucomatocyclitic crisis and late developmental glaucoma

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The signs of congestion had disappeared Keratic precipitates had been partly visible

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X CHROMOSOMAL RECESSIVE RETINOSCHISIS IN THE REGION OF PORI

An ophthalmo genetical analysis of 103 cases

BY

BIRGITTA VAINIO MATTILA A. W ERIKSSON
and H FORSIUS

As far as can be judged by the number of cases so far published X chromosomal recessive retinoschisis is a relatively rare disease The first to describe a case was *Thomson* in 1939 Since then somewhat over 100 patients have been described Previously the disease was named cystoid degeneration of the retina or macula It was described in detail by *Ida Mann and Macrae* in 1938 Its X linked recessive heredity was clarified by *Levy* in 1952 and *Jager* in 1953 The name retinoschisis was introduced in 1953 by *Franceschetti* who thus wanted to define the disease as a splitting of the retina into two layers Apart from our patients only 11 cases have been reported in Scandinavia All of these patients described by *Bengtsson and Linder* in 1967 belonged to either of two families Recently two cases have been published by *Yanoff Kertesz and Zimmermann* In a family with eight children all of whom were boys six sons had normal eyes while two had bilateral retinoschisis One affected eye was histopathologically examined *Lisch* 1968 described 4 retinoschisis cases in a large family

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Dedicated to Professor Bertel von Bonsdorff M D Fourth Medical University Department Helsingfors on the occasion of his 65th birthday

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Retinoschisis is the name used for a process in which cystic degeneration of the retina causes a cleavage of the different retinal layers As a result of this degenerative process the superficial layer of the retina may become detached from the underlying tissue or it may peel off According to *Yanoff et al* in juvenile retinoschisis cleavage of the sensory retina usually occurs in the layer of nerve fibres This is in contrast to senile retinoschisis in which the splitting occurs in the outer plexiform layer and in the adjacent nuclear layers of the retina

The disease shows wide variations in regard to clinical picture and degree of severity even affected members of the same family differ in this respect We have classified our cases according to the degree of severity as 1) mild 2) moderate 3) severe

1 Mild cases

The changes are mainly localized to the region of the fovea In this site a wheel like formation about the size of a papilla is seen which results from creasing of the superficial retinal layer (Fig 1) In rare cases this cystic formation may rupture and minute haemorrhages may be seen as a rule at the centre of the wheel like formation The haemorrhages are due to rupture of the blood vessels in the superficial layer of the retina concurrent with rupture of the cystic wall The creasing in the region of the macula is best seen in red free

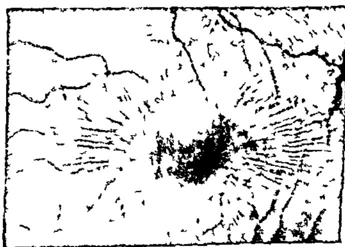


Fig 1

Cystic foveal degeneration with radial radiation of the superficial retinal tissue in a year old boy Degree I

light These radial streaks are highly typical and readily distinguished once one has learnt to recognize them However changes are not invariably present in the region of the macula In rare cases only slight changes are seen Then the diagnosis presents problems and it is necessary to inquire closely into the family history since confirmed cases of retinoschisis among the patient s relatives on the maternal side lend support to a suspicion of retinoschisis

2 Moderate cases

The moderate cases show semi translucent vitreous sails in addition to the changes described above These sails are detached portions of the superficial layer of the retina They are most often encountered temporally below in the vitreous body and may remain unchanged for decades The sails may float freely in the degenerated vitreous body but as a rule they appear elevated from the ocular fundus form coherent veils and seem to extend from apparently normal retinal tissue (Fig 2) Retinal blood vessels may be demonstrated in them obviously originating in the normal retina The veils often exhibit holes surrounded by retinal blood vessels The sails show wide variations in

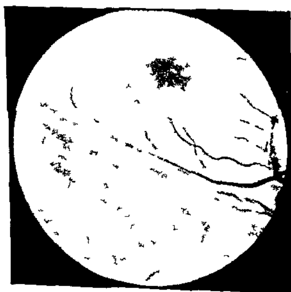


Fig 9
Detail of eye ground showing X chromosomal retinoschisis Cystic foveal degeneration is seen above a projecting fold of the retina below The patient is a 25 year old male
Degree 2

appearance Sometimes they form rolls or streaks in the vitreous body Haemorrhages in the ocular fundus or the vitreous may occur Just as in the mild cases they are due to rupture of retinal blood vessels in connection with detachment of the superficial layer of the retina

With Goldmann's 3 mirror contact lens white garland like formations are nearly always seen in the peripheral portions of the retina

3 Severe cases

There are various other symptoms as well when the lesion is severe Drusen of the optic disc may be seen adjacent to or on the papilla and the latter may be atrophied In addition whitish streaks may be seen along the blood vessels of the retina These are probably due to some kind of glial reaction Degenerative changes are encountered in abundance in the various layers of the retina and also in the choroid Usually only the superficial layers of the retina are detached but true" detachment of the retina may also occur Occasionally and particularly in advanced age the disease may lead to total destruction of the retina and blindness

Clinical course

The disease under discussion is obviously congenital One patient in the present series has been practically blind since birth and we have seen the wheel like formation in the macula of an infant aged 1½ years



Fig 3

Detail of eye ground in a 25 year old male showing almost complete destruction of the retina and choroid Degree 3

In mild cases impairment of vision is usually observed at compulsory examination of the eyes at school Acuity of vision in these children ranges from 0 1 to 0 6 Vision may remain fairly constant for several decades

Slight variations may occur improvements alternate with exacerbations indicating a continuous process in the region of the macula Fresh ruptures and minor haemorrhages alternate with partial healing of earlier lesions

The progress of the disease is very slow However in patients over 50 years of age we have observed that the degenerative process is far advanced and the clinical picture in these cases resembles the one seen in senile sclerosis of the eye grounds As a rule the wheel like formation has disappeared At the site of the cystic degeneration there is a dry shiny atrophic focus clearly demarcated from the surrounding tissue and darker in colour than the surrounding retina In these cases the diagnosis is greatly aided by inquiry into the previous history and the family history As a rule the patient gives a history of impaired vision since childhood If an uncle on the mother s side or a son of the patient s daughter s shows retinoschisis this constitutes reliable corroborative evidence Most of our 50 year old retinoschisis patients have a visual acuity of 0 1 There is one exception to this rule i e a 44 year old man with confirmed retinoschisis classified as mild He has a typical macula and several relatives with confirmed retinoschisis and his visual acuity is 1 0 on both eyes

Our series in the Pori region includes two almost completely blind patients One of them is a woman who to the best of our knowledge is the only genealogically genetically and clinically verified homozygous case described in the literature (*Forsius et al* 1962 1963)

Results of examination

As previously mentioned visual acuity is usually though not invariably impaired The visual fields are unexpectedly large This seems to indicate that some function remains even if the retina is seemingly destroyed Colour vision shows secondary changes varying in degree from slight to marked Hereditary dyschromatopsia (deuteranomaly) has hitherto been detected in only two of our retinoschisis families The ERG is slightly subnormal In severe cases it may even be extinguished Dark adaptation is impaired by about 1 2 log units

The vitreous body is often degenerated as a rule to the same degree as the retina On fluorescein angiography the mild cases show no after fluorescence in the wheel like macula This is in contrast to the finding in cases of macular degeneration associated with chronic cyclitis In severer cases the choroid shows a certain degree of granularity The severer the changes in the retina the more

conspicuous the part played by the choroid in the extravasation phase of angiography

Treatment

It has been stated in the literature that photocoagulation is of help in retinoschisis of various etiologies in which progression of the peripheral detachment of the retina has been observed

The border between the detached and undetached retinal tissues is coagulated Cases showing true ablatio retinae can be operatively treated by current techniques One patient in the present series was successfully treated in this way

Heredity

The type of retinoschisis under discussion is an X chromosomal recessive disease It is inherited from affected fathers via seemingly normal daughters (in one or more generations) to their sons Our series includes one female patient (*Forsius et al* 1962 1963) the strange product of a marriage between cousins who are related in two different ways The patient s father has retinoschisis and her mother is a conductor Her three sons by two husbands all have retinoschisis

Our material includes a number of pedigrees in which we have been able to follow the heredity of the disease on the basis of its clinical manifestations through three or four generations Most of our families have presented a verbal tradition or written evidence that male members in the more distant ascendancy had poor vision (highly near sighted) already as relatively young or this information was obtained from parish or tax registers Since in the region of Pori trachoma and similar diseases have not been epidemic and the frequency of cataract glaucoma and degeneratio retinae pigmentosa is not exceptionally high retinoschisis may be considered the cause in the majority of cases in which impairment of vision has been recorded at least as far as young men are concerned

Microsymptoms in carriers

In view of the Lyon hypothesis of random inactivation of one of the two X chromosomes in females one would expect to find symptoms in the retinoschisis

carriers The female heterozygotes so far carefully investigated (with mirror contact lens etc) seem to be quite normal however

In some elderly retinoschisis carriers we have observed macular degeneration or peripheral retinoschisis The changes are usually bilateral So far we have found only one male with unilateral retinoschisis Further investigations are in process to find out whether these carriers show formes frustes of retinoschisis or senile changes It may however be mentioned that we have seen peripheral retinoschisis also in old fathers of retinoschisis patients

Linkage

The retinoschisis locus on the X chromosome is at present a candidate for measurable linkage with the locus of the Xg blood group The six families giving linkage information argue in favour of the assumption that the retino schisis locus is not close to that for Xg (*Eriksson et al* 1967 *Race and Sanger* 1968) In the two retinoschisis families with deuteranomaly the retinoschisis and deutan loci seem not to be closely linked

Sex ratio

In the initial stage of our investigations we observed that males were predomi nant among the offspring of retinoschisis carriers We thought to begin with that this was due to chance or that families with many affected boys were more likely to attract attention

Studies performed mainly in the area of Pori have shown that among 304 children of 55 retinoschisis carriers after omission of 26 male propositi the secondary sex ratio is extremely high 167 100 (*Eriksson et al* 1967 b)

Differential diagnosis

Owing to the variations in the course and clinical picture X chromosomal retinoschisis is likely to be erroneously diagnosed as some other disease in which similar degenerative changes of the retina occur e g periphlebitis retinae To distinguish retinoschisis from sclerotic degeneration of the retina in elderly men a genealogical approach to the history and heredity is re quired The difference between X chromosomal retinoschisis cysts of the

retina true ablation and senile retinoschisis is not always obvious Diagnostic mistakes are easily made and is is therefore *probable that many cases are* erroneously classified

When young men show changes of the vitreous or retina cystic degeneration of the macula haemorrhages in particular in the vitreous or detachment of the retina the possibility of retinoschisis should always be considered It is often advisable to examine the remainder of the family as well The family history may be an aid in diagnosing the disease and if a correct diagnosis is made it is easier to make a reliable prognosis

In the literature the disease has been described under various names *Juler* 1948 *Sorsby et al* 1951 and *Magnus* 1951 described it as a form of true ablation of the retina *Sabates* 1966 pointed out that ablation temporally below is the commonest form of detachment in patients less than 25 years of age The differential diagnosis between retinoschisis and this form of retinal dialysis which also is more common in men than in women is not always easy

Sabates states that long-standing retinal detachment tends to cause cysts in the retinal layers and that cysts are a characteristic finding in this type of detachment In addition a pigmented line of demarcation may be seen between the detached retina and the undetached portion This line of demarcation *may extend as far as the macula* and it may cause *disturbances in the* chorioretinal pigmentation

Veils in the vitreous body are also seen in the dominantly inherited Wagner s degeneratio hyaloideo retinalis and in Goldmann Favre s degeneratio hyaloideo tapeto retinalis In these veils there are no blood vessel however and the structure of the *vitreous* is unchanged *(Richi* 1961) *Bengtsson and Linder* 1967 emphasize that many of their cases have previously been diagnosed as macular degeneration or chorioretinitis of unknown etiology

Geographical distribution

Up to the beginning of 1969 we had diagnosed over 130 cases of X chromosomal retinoschisis in Finland A total of 103 of these patients come from the county of Satakunta in southwest Finland and the majority of these and their mothers come from the town of Pori (in Swedish Bjorneborg) and particularly from the surrounding rural communes north of the town To obtain a better idea of the origin of the disease and to eliminate the effect of migration we have inquired into the places of birth of the carriers whose descendants have *developed X chromosomal retinoschisis* (Table I and Fig 5)

It should be noted that northern Satakunta i e the district northeast of Pori consists of sparsely populated woodland The communes are relatively poor and the supply of work is very *limited There ha been hardly* any migration to the district and the younger generation is drawn to the centres

Table I

Detected retinoschisis carriers and their affected son distributed according to the birth parish of the carriers

As carriers have been included only mothers born in the region of Pori with at least one son showing retinoschisis diagnosed by an ophthalmologist Only patients with retinoschisis diagnosed by an ophthalmologist have been regarded as affected sons The frequency of carriers has been calculated on the census of 1930

Parish	Carriers		Affected sons
	Number	Per 10 000 inhabitants	Number
Noormarkku	14	30.3	21
Pomarkku	7	14.5	12
Lavia	8	14.[illegible]	16
Ahlainen	4	9.6	5
Siikainen	3	5.5	4
Eura	2	4.8	2
Town and rural commune of Pori	13	4.8	20
Karvia	2	4.1	3
Merikarvia	3	3.5	6
Kiikoinen	1	3.3	1
Ulvila	[illegible]	2.2	3
Tyrvaa	2	2.1	7
Parkano	1	1.3	2
Kokemaki	1	1.3	1
Total	63		103

of population in the first place to the town of Pori which offer better chances of finding a job

Noormarkku Pomarkku and Lavia have the highest frequency of carriers A large number of carriers come from the village of Lassila in the parish of Noormarkku close to the border of Pomarkku According to the church register numerous men living in this village in the eighteenth and nineteenth centuries were blind or had poor vision We have been able to trace many of our families as far back as the seventeenth century These genealogical studies have revealed that many of the retinoschisis probands are descended from farms concerning which the church or tax registers contain a note that the men had impaired vision or were blind (Fig 5)

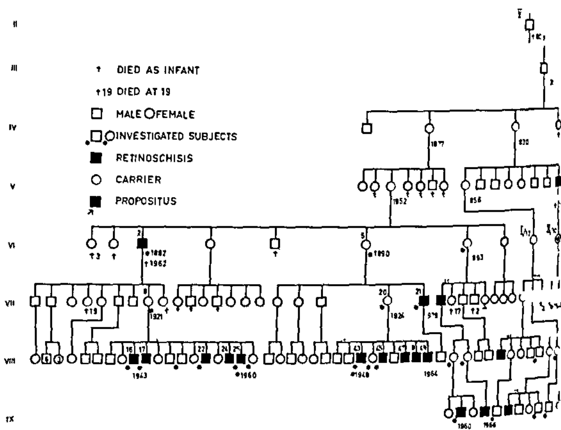


Fig 4

Discussion

Since X chromosomal retinoschisis seems to be a rare disease only some 100 cases having so far been published the question may be posed as to why we have detected such a large number of cases in the region of Pori Owing to the lack of specialists the school children with impaired vision in this region have for many years been examined by one and the same ophthalmologist (B V M) who is interested in retinoschisis and on the alert for this disease In general our retinoschisis patients have shown a remarkable mind for family connections and they have co operated actively in tracing similar cases among their relatives

Of the detected Finnish retinoschisis carriers over 75 per cent come from the Pori region The population in this region from which the mothers of the

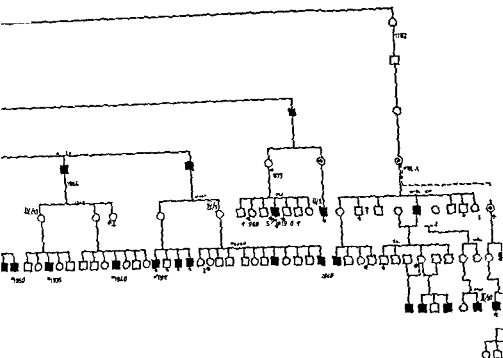


Fig 4

Pedigree showing the genealogical correlations between some retinoschisis families descending from the village of Lassila in Noormarkku in the region of Pori

103 retinoschisis patients come constitutes about 5 per cent of the total Finnish population Either has this high *frequency of* retinoschisis been observed be cause the local ophthalmological department has been specially interested in this disease *or is it a result* of a real concentration of retinoschisis The growth of the population has been relatively rapid during the last century The social structure was previously very stable and there was little migration in some areas The majority of patients with retinoschisis have a visual acuity which allows them to work in many occupations until the age of 40 60 years Since no other defects have been discovered in connection with the retino schisis gene it may be assumed that this disease was not in the past either a handicap likely to appreciably reduce the chances of making a family On the other hand we have not observed any selective advantages of the retinoschisis gene The various communes in the carefully investigated region of Pori show

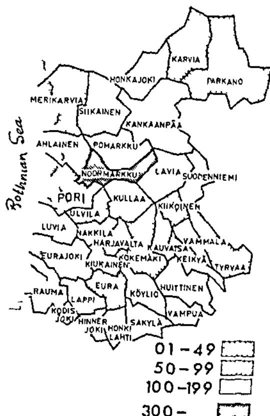


Fig 5
Map showing the distribution and frequency of detected retinoschisis carriers according to their birth parish in the Pori/Bjorneborg region The calculations are made on the population census Dec 31 1930

different frequencies of the retinoschisis gene Considering the above mentioned facts it would seem that the high concentration of retinoschisis observed in the isolated backwoods north of the town of Pori is real and due to chance (founder effect)

Summary

So far only some 100 males with X chromosomal recessive retinoschisis have been described During the years 1956 1968 103 cases (1 homozygotic female and 102 hemizygotic males) with X chromosomal recessive retinoschisis were diagnosed in the county of Satakunta in SW Finland All these subjects lived in this county or had maternal ancestors in either of the two preceding generations who came from Satakunta The frequency of detected carriers with one

or more boys with retinoschisis is particularly high in the rural parishes north east of the town of Pori/Björneborg

In the maternal ascendancy of the retinoschisis probands so far studied the church or tax registers or both exhibit an accumulation of males with re corded blindness or poor sight Both mild and severe cases can be found in the same family The youngest diagnosed retinoschisis patient was 1½ years old The main symptoms in the subjects with X linked retinoschisis are poor sight radial cystic macular degeneration and peripheral superficial retinal detach ment Vacuolization of the vitreous body was observed in almost all of the af fected adults Adult patients in particular have secondary colour vision defects and moderately disturbed dark adaptation Our observations are indicative of a functional disturbance of both the rods and cones of the retina

Owing to the X chromosomal heredity with skipping in generations and the progression with variations in the course and clinical pattern X chromo somal recessive retinoschisis may be erroneously diagnosed Hence it is possible that this disease is not so rare as the small number of recorded cases would suggest

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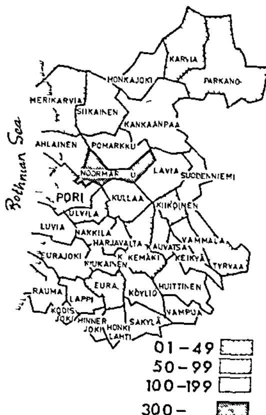


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TONUS OF THE CILIARY MUSCLE DURING SLEEP

BY

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The miotic pupil during sleep is a well known phenomenon but the mechanism has so far been incompletely analysed Information on the tonus of the para sympathetic ciliary muscle is on the whole lacking The state of the ciliary muscle during sleep is of physiologic interest particularly with reference to effects on the outflow resistance

Some methodological factors have to be considered in an investigation of this problem A study of the tonus of the ciliary muscle restricts the material to primates Induced sleep with general anesthetics is not acceptable since it may very possibly have central and local eye effects different from those in physiological sleep In the present investigation the experimental material was selected from human subjects with a high arousal threshold (i e children) and who were examined during a defined period of sleep by retinoscopy

Physiology of sleep Sleep is not a uniform condition In humans two principal types of physiological sleep are distinguished At the onset of sleep slow cortical waves with big amplitude and sleep spindles appear on the EEG The muscle tonus diminishes the blood pressure the pulse rate the respiratory frequency and the temperature decrease Sweat and gastric secretion increase salivation decreases and peripheral vessels dilate In the pioneer work on sleep by Hess[8, 16] some of these physiological data were taken as evidence of a generally increased parasympathetic activity during sleep This synchronized sleep is interrupted after 1 2 hours for a period of 10 15 minutes of desynchronized sleep This period is characterized by the appearance of fast waves with small amplitude on the EEG Fluctuations in blood pressure pulse rate and respira

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cludes the outer and inner eye muscles [5] In the oculomotorius nuclear complex in the monkey a discrete mass of cells for accommodation and a smaller mass of cells for pupil constriction were established [3, 11] Accommodation or accommodation together with a varying amount of pupillary constriction were more often produced than an isolated constriction of the pupil [11]

Material and Methods

The investigation was performed during a period of "synchronized sleep 1 2 hours after the onset of sleep The material comprised children generally 2 5 years of age healthy or treated for a non ophthalmological disease in a pediatric department Only this age group showed a sufficiently high arousal threshold to permit the examination The refraction and indirectly the tonus of the ciliary muscle was determined with streak retinoscopy [1] using a Keeler retinoscope and a working *distance of 0 5 m Determinations of the refractions* were done with lenses to the nearest half dioptri Retinoscopy was performed on the same subject on two separate occasions firstly during physiological sleep and secondly in the awake state in cycloplegia (2 drops oof a 0 5 *per cent* atropine solution were instilled three times prior to the examination) In the examination during sleep all subjects were double examined that *is both* examiners carried out the examination on the same occasion without *causing an* arousal of the test subject The tendency to arousal restricted in most cases the examination to a qualitative estimation i e an against" movement or a *with movement* In a few cases it was possible to perform a quantitative retinoscopy Difficulties in carrying out the examination *on account of the* sleeping position the position of the eyeballs or the arousal tendency *led to a* very high rejection percentage In all about a hundred children were examined and on an average nine out of every ten subjects were discarded

It should be possible to raise the eyelid without resistance Miosis served as a control of sleep *The pupil dilated* immediately on arousal The examiners aimed at a central *retinoscopy but sleeping* position and position of the eyeballs might in some cases have induced a small angle error Tests with awake normal subjects with a miotic pupil (? 3 mm) showed that an angle error of 10° gave a change of refraction of less than 1 D *Spherical* aberration in a dilated pupil causes a refraction change of several dioptries [18] Thus with reference to spherical aberration and *oblique astigmatism* the miotic pupil is favourable A possible fixation of the examined eye on the retinoscope would lead to a refractive increase A fixation would evoke *a nystagmus* response in subjects exposed to an optokinetic stimulus This response is obligatory in awake subjects despite an optical distortion oof the stimulus greater than that which might be present

tion are common An episodic appearance of rapid eye movements often synchronous with dreaming is a characteristic phenomenon[1] After the REM period (Rapid Eye Movement) slow cortical waves reappear and the course is repeated The depth of sleep with regard to the EEG pattern undergoes cyclic variations during the night High arousal thresholds occur in periods of pronounced synchronized sleep as well as during REM Individual variations are common with a prevalence for higher threshold values during the early hours

The eye during sleep The closure of the lids is considered to be a tonic contraction of the orbicular musculature together with an associated inhibition of the levator muscle[8, 10] Real evidence however seems to be lacking[15] and lid closure is not an obligatory phenomenon[6] In favour of an active contraction is the fact that the eye is not closed in facial nerve paralysis The conjunctival vessels are usually moderately dilated Even if there is no characteristic eye position during sleep the eyes usually seem to be directed upwards and outwards Pietrusky[16] noted a central position in only 13 % a position upwards in 23 % and a divergent upward position in 46 % Investigations on the position of the eyes are performed in periods of "synchronized" sleep when also slow driving movements of the eyes are recorded Slow eye movements during physiological sleep have been compared to the slow eyeball movements observed during light anesthesia[5] This activity decreases with increasing depths of narcosis until it finally ceases

Earlier observations of slow eye movements were confirmed during continuous measurements throughout the night when also periods of rapid eye movements were registered[1] Rapid activity is dramatic and might be observed through closed eyelids It is correlated to the active phase of the cortex The constriction of the pupil during sleep is so characteristic that it can be used to differentiate true from simulated sleep The constriction of the pupil is more pronounced in children and increases with increasing depth of sleep The light reflex is preserved The origin of the miotic pupil during sleep is still a matter of controversy[13] It seems however less likely that the miosis might be due to changes in the sympathetically innervated dilator muscle by lack of stimuli from the cortex to the sympathetic center Berlucchi et al[4] showed that the constriction of the pupil during sleep remained intact after a preganglionic sympathectomy and they ascribed the sleep miosis to a hypertonus Edinger Westphal nucleus It is usually assumed that the miosis is caused by shutting off inhibitory impulses from the cortex to the constrictor center In the awake state it is supposed that the cortex continuously inhibits the activity of subcortical centers Lack of cortical inhibition during sleep allows subcortical centers to prevail resulting in a miotic pupil[14] It is probable that the cortical inhibition is not restricted to the center of pupillary constriction The miosis and the slow eye movements of the eyeball during physiological sleep and light anesthesia have been ascribed to an increased activity in the nuclear complex which in

were in agreement In children who awoke during the examination the pupil immediately dilated and an against movement could be observed to change to a with movement These cases are not taken into account in table I since they did not fulfill the criteria that both examiners should be able to carry out the examination Rejection of test subjects was due to arousal or change of sleeping position and in no case due to the fact that it was possible to carry out the examination but that the examiners had differing results

Discussion

In order to avoid a subjective estimation and to restrict methodological errors we considered it necessary that the two examiners should have been able to carry out the examination on the same occasion These conditions and the low arousal threshold of the test subjects caused a high rejection percentage The remaining cases are few but they differ from the others in only one respect i e a high arousal threshold Because this is the only difference they can be considered representative for this age group The results from successful cases are so unequivocal that one might be entitled to conclude that at least in the examined age group the ciliary muscle is contracted during physiological synchronized sleep This fact together with the constricted pupil during sleep points to an activity in that part of the oculomotorius nucleus where the centers for pupil constriction and accommodation are localized This is in agreement with the opinion of Lowenstein & Loewenfeld[14] that the miotic pupil during sleep is caused by oculomotory activity from cortical inhibition Jampert & Mindel[11] also found that although they could isolate different cell groups for constriction of the pupil and accommodation an isolated pupillary constriction was only rarely produced

At first it was believed that the observations on contraction of the ciliary muscle during sleep were original However Poos[17] in 1949 a sumed from the hypothesis of a *generally* increased parasympathetic activity during sleep that the ciliary muscle also should be contracted *He attempted* to measure the refraction during sleep but could only report one successful case a child who showed an increase of the refractive power *of the lens of 4 5 D* during sleep

A contracted ciliary muscle during sleep might be of importance to the resistance of the chamber angle and the facility of aqueous outflow during the night However the present investigation did not permit conclusions on this subject since the technique used did not allow an examination of the more interesting older age groups The clinical observation that cholinesterase inhibitors prescribed at bedtime are in fact effective might have its explanation if there were a liberation of acetylcholine from an active ciliary muscle

during sleep During sleep no optokinetic nystagmus response however can be evoked This indicates that fixation during sleep of an optical stimulus like the retinoscope is not likely Nor is it probable that physiological "synchronized sleep is transferred to a REM period from optical stimulation Dream images could not be evoked from light stimulation in sleeping subjects[18] In the present investigation *rapid eye movements were in no case provoked by the examination*

Results

The results are summarized in table I All of a total of nine successful cases showed an increase of refractive power during sleep In 3 cases this increase could be quantitatively estimated and amounted to 4.8 D Also the qualitatively examined cases permitted a crude analysis of the increase in refractive power Since an "against" movement is evidence of at least a refraction of −2 D the mean refractive power increase during sleep compared to the cycloplegic state amounted to at least 3 D *In all cases the pupils were miotic* and in 6 cases there was a pronounced conjunctival injection The results from both examiners

Table I

Miosis conjunctival injection and refraction during sleep and cycloplegic refraction in the awake state in children

Case		Age Years	Conjunctival *injection*	Miosis	Streak retinoscopy at 0.5 m		
					During sleep		Cycloplegic refraction
					Movement against ← with →	D	D
C L	♂	[illegible]			←		0
R W	♂	5	+	+	←		+1.5
A L	♀	5	+	+	←	−8.0	0
M E	♂	5	+	+	←		0
P A	♀	4		+	→	+1.0	+5.0
G A	♂	4		+	←		+2.0
A S	♀	3	+	+	←	−3.0	+1.5
E W	♀	2	+	+	←		+1.5
M W	♂	3	+	+	←		+0.5

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Summary

Children were examined by streak-retinoscopy first during physiological sleep and secondly in the awake state in cycloplegia A great majority of the test subjects were discarded due to a low arousal threshold In the nine successful cases an increase of the tonus of the ciliary muscle during sleep was established This increase was on an average at least 3 D and in three cases who were quantitatively examined it amounted to 4 8 D compared to the cycloplegic refraction A constricted pupil was found in all cases The results indicate that during sleep there is a stimulation (presumably by cortical inhibition) of those parts of the *oculomotorius nucleus which control the sphincter and the ciliary muscle* A contracted ciliary muscle during sleep might possibly affect the outflow resistance of the eye

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uncooled diathermy is that the surface layer of sclera does not dry and loose its conductivity so that the current is automatically broken With psychrodiathermy the burning can therefore be continued for longer and with greater penetration

If the effect of coagulation is observed in the surface layer clinically this can therefore not give an indication of the effect in deeper layers and the aim of this investigation is to study histologically the destruction in the layers of sclera choroid and retina Two questions are of special interest

How intense is the effect of psychrodiathermy compared with conventional diathermy in different layers of the sclera and most important in the choroid?

Is it possible to demonstrate histologically that destruction produced by psychrodiathermy is less pronounced in the superficial layers of the sclera than in those more deeply placed?

Material and Methods

Pigmented rabbits have been used for in these animals the ophthalmoscopic appearances most clearly resemble those seen in man In one series three animals have been used and four in the second series Both eyes have been used In the first series one eye perforated with diathermy coagulation and this has been excluded

The experimental coagulations have been carried out under anaesthesia with Nembutal 40 mg/kg The diathermy burns have been made with a ball electrode 1 0 mm in diameter After preparation of the conjunctiva coagulations have been performed at the equator from 9 30 11.30 and 12.30 14 30 Within each of these areas the coagulations were of the same type but each area represented a different coagulation technique in order to compare the tissue changes in the same eye

The diathermy setting has been different in the two series In the first series a low setting has been used (about 25 mA)* which with uncooled diathermy has been applied for a coagulation time of 9 seconds producing a visible ring of coagulation around the electrode With psychrodiathermy the time has been lengthened to 12 seconds The long coagulation time in this series has been used with the aim of making possible a more certain adjustment of the effect

In the second series a more usual setting of the apparatus has been used (about 40 mA) which with this electrode (1 0 mm) has produced definite coagulations in 3 seconds with conventional diathermy Using information derived

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* The apparatus was not provided with an Ammeter and the mA values are derived from the settings and obtained with comparative trials on liver tissue

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STUDIES ON THE HISTOLOGY OF TISSUE DESTRUCTION PRODUCED BY SURFACE DIATHERMY AND PSYCHRODIATHERMY IN THE RABBIT EYE

BY

BENGT ROSENGREN PATRICK SOURANDER
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Cooling of the sclera in association with diathermy burning – here termed psychrodiathermy – can be produced by dropping ice cold distilled water on the sclera The coagulation process is thereby changed in character

With diathermy the high frequency electric current passes between the small active electrode and the larger inactive electrode By drawing approximate lines of current it is possible to obtain an idea of the distribution of the current It can be seen how the lines of current are closest under the small active electrode and it is here that the most intense heat is produced decreasing as the lines of current spread out in the tissues With surface diathermy of the sclera – until recently *the usual method in detachment surgery – the heating is thus most in*tense in the superficial layer of the sclera with the intensity decreasing in the more deeply placed tissue layers

If the sclera is cooled the heat produced by the current is conducted from the surface layer to the cooled fluid and the fluid cooled electrode and the result is that only centrally under the electrode where the lines of current are closest does a grey discolouration of sclera indicating coagulation appear From there the coagulation effect extends towards the deeper layers and this can be demonstrated in tests on liver tissue An important difference from conventional

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Choroid The tickness was increased because of plasma leakage Widespread fresh haemorrhages Disintegration of pigment epithelial cells with extracellular pigment dispersion
Retina Marked destruction partly adherent to the choroid

Coagulation with psychrodiathermy

Sclera Intact except that the boundary with choroid in places obscured with slight pigment migration in the deeper layers
Choroid Slight thickening with dilated vessels In one of these an aggregation of platelets as a sign of clot formation (Fig 2) No definite haemorrhage No sign of inflammation Numerous migrated pigment cells
Retina Without obvious changes

Series II

Coagulation with diathermy

Sclera No changes in some sections In other sections areas with lost staining



Fig 9
Psychrodiathermy 12 sec 25 mA slight changes mainly in choroid

from the results in the first series the time for psychrodiathermy has been increased to 6 8 seconds After burning it has been determined ophthalmoscopically that grey discoloration has occurred in the retina

Enucleation has been performed after 12 days in the first series in the second series after 8 days The eyes have been placed in 10% Formalin and fixative fluid has also been injected into the vitreous cavity In the first series the eyes have not been embedded whole but only the areas of coagulation which however were associated with an increased tendency to detachment In the second series the eyes have been embedded in paraffin after removal of the cornea lens and posterior pole At the operation a silk suture was inserted in the 12 o'c meridian from a point behind the equator to a point near the limbus as suggested by Dr Ry Andersen and this has been easily identified in the histological preparations and has been valuable for orientation

Section thickness 10 μ staining with v Gieson s mixture

Results

Series I

Coagulation with diathermy

Sclera The fibres were somewhat poorly defined but with retained staining properties No inflammatory cell infiltration In the deep layers there was migration of pigment cells the boundary with the choroid was poorly defined (Fig 1)



Fig 1

Diathermy 9 sec 25 m A changes in sclera choroid and retina



Fig 4
Psychrodiathermy 8 sec 40 mA fading mainly in the deeper scleral layers

but no obvious haemorrhage The treated area contained melanin pigment throughout partly within phagocytes partly extracellular No evidence of fibroblastic proliferation with deposition of collagen No inflammatory cell reaction

Retina Markedly thinned and detached in the treated area but adherent at the edge of the lesion

Discussion

Firstly in the comparison between diathermy and psychrodiathermy the choroid may conveniently be studied It is from this tissue that the reparative adhesive tissue proliferation is derived which essentially leads to adhesion between retina choroid and sclera

It can be established that in the rabbit eye the effects of diathermy and psychrodiathermy are most different if the diathermy *current is applied* for approximately the same length of time (Series I) While it is fully developed following diathermy it is only suggested with psychrodiathermy In Series II therefore it was decided to use rather more than double the coagulation time for psychrodiathermy The effect then is about the same or possibly somewhat less marked with the latter method of coagulation There is no evidence of a different type of destruction The reduced destruction of small vessels with psychrodiathermy can best be regarded as a sign of a less intense effect on the tissues

properties and dissolution of the fibrillar structure (Fig 3) Marked increase in cell nuclei Some cells show degenerative signs others are of fibroblastic type with large nuclei and prominent nucleoli consistent with proliferation In the periphery of the lesion vascular dilatation and small haemorrhages In the superficial layers slight inflammatory reaction
Choroid At the sites corresponding to the coagulations there was marked *thickening* *Within* these areas numerous very dilated capillaries and veins filled *with* packed erythrocytes Perivascular collections of erythrocytes The structure *of the* choroid markedly loosened probably resulting from plasma leakage *Throughout the* treated area melanin pigment partly included in pigment pi thelial cells and phagocytes partly lying extracellularly No *obvious increase of* inflammatory cells or fibroblastic proliferation
Retina Converted to a thin membrane which at the periphery of the lesion was adherent to the choroid

Coagulation with psychrodiathermy

Sclera in the area of the lesion showed a decrease of the staining intensity (de creased fuchsinophilia) The fibrillar structure loosened and the cell nuclei to a great degree retained but with degenerative changes No inflammatory reaction The lesion in the sclera was most marked in the deeper *layers* *adjacent* to the choroid and less pronounced in the superficial layers (Fig 4)
Choroid Thickened corresponding to the coagulated area The normal struc ture loosened Capillaries and small veins moderately dilated in many areas



Fig
Diathermy 3 sec 40 mA fading in different layers of sclera

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EXCITATION OF PHOTORECEPTORS

A Review

BY

LARS WALLØE

In 1942 Hecht Shlaer and Pirenne showed that single photons can excite dark adapted human retinal rods Later the one quantum hypothesis has been strongly supported also for the compound eye How is this tiny amount of energy in one light quantum converted into a sensory message? This question will be the topic for this article

The first step in this excitation process is the absorption of the light quantum in a pigment molecule in the photoreceptor cells Some of the visual pigments in vertebrate eyes are shown to be proteins with *retinene* as a prostetic group Retinene containing proteins are also shown to be the visual pigments in photoreceptors in such different phylia as flat worms molluscs and arthropods In other photoreceptors for instance in the three different primate cones the visual pigment are not yet chemically isolated and investigated but spectroscopic evidence indicate that also these photopigments are proteins and contain retinene

The pigment molecules are always located in a specialized part of the photoreceptor cells with a highly regular fine structure In the vertebrate eyes these photoreceptor elements are the *outer segments* of the rods and cones These outer segments are composed of submicroscopic plates orderly disposed in a pile as shown on Fig 1 Each disk is about *150 Å* thick Similar structures are found in the visual cells in flat worms whereas closely packed thin walled tubes build up the light absorbing structures the rhabdomeres in the visual

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With regard to the destruction of sclera a comparison of its localisation with the different coagulation procedures can be studied firstly by decreased staining intensity in various areas As enucleation has been performed after 8 days and fibroblastic proliferation can be seen the decreased staining intensity should indicate essentially that repair stage has not progressed to the point when collagen has been formed

In certain cases of diathermy coagulation a decrease of the fuchsinophilia is very pronounced and it extends through all layers of the sclera At the psychro diathermy coagulation sites similar changes can be seen There is however an impression that the decreased fuchsinophilia appears essentially in the deeper layers of the sclera This agrees with the clinical observation that the superficial layers of the sclera are relatively slightly affected

Conclusions

If the sclera is cooled during diathermy coagulation the coagulation time must be rather more than doubled in order to produce the corresponding effect in the choroid With this form of diathermy the surface layers of the sclera are spared

Acknowledgements

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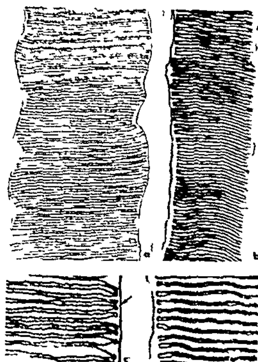


Fig 1
Longetudenal section through a vertebrate rod (b d) and cone (a c)
From Dowling (1967)

cells in molluscs and arthropods Fig 2 shows a transverse section through the tubes

The chemistry and biochemistry of visual pigments especially rhodopsin are known in great detail due to the works of Georg Wald and his co workers at Harvard Retinene is an aldehyde In rhodopsin retinene is bound to the protein opsin in a Schiff base linkage by the condensation of the aldehyde group of retinene with an amino group of opsin The amino group is recently identified as the ε NH group of a lysine unit The amino acid sequence of some large parts of the opsin molecule is also determined Cattle rhodopsin has a molecular weight of about 40 000 The molecule has a shape not far from spherical and the diameter is about *40 Å* The retinene molecule is about *20 Å* long It looms surprisingly large therefore in the structure of rhodopsin And the rhodopsin molecules are again large compared to the thickness of the outer segment disks It is therefore suggested that the pigment molecules are oriented as monolayers in the disks that is with two pigment molecule layers in each disk It is also suggested that a similar monolayer covers the walls of the tubes in arthropod and mollusc eyes

Rhodopsin contains retinene with cis configuration around the double bond

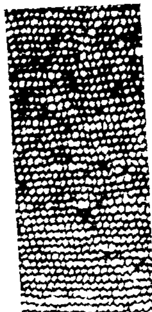
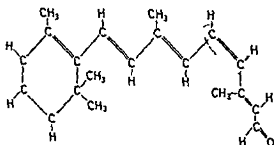


Fig 9

Transverse section through the tubes of an arthropod rhabdomere From Miller (1957)

between carbon atom 11 and 12 (Fig 3) Light isomerizes the 11 cis molecule around this double bond to the all trans configuration The first product is pre lumirhodopsin (Fig 4) which is stable only below about − 140° C On warming above this temperature in the dark prelumirhodopsin goes spontaneously to a



11 CIS RETINENE

Fig 3

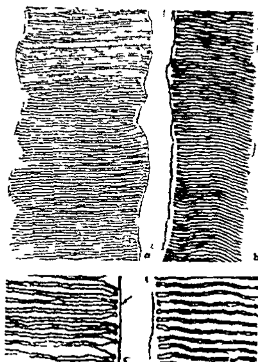


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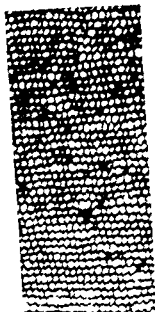
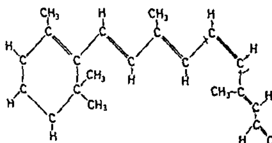


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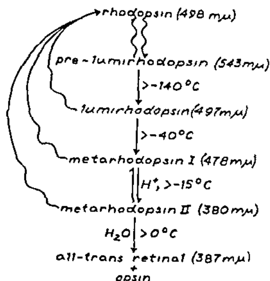


Fig 4
From Wald (1968)

second chromoprotein lumirhodopsin which is stable up to about $-40°$ C Above this temperature lumirhodopsin is converted to metarhodopsin I which is stable up to about $-15°$ C Above this temperature it enters into equilibrium with metarhodopsin II Finally on warming above $0°$ C metarhodopsin is hydrolyzed to all trans retinene and opsin probably through some other intermediates

These chemical reactions are studied in great detail on rhodopsin from such different sources as cattle and squid The results are quite similar Similar reactions and intermediates are also found in the bleaching of the cone pigment *iodopsin from chickens*

Although these chemical reactions are usually studied at low temperatures in rhodopsin solutions there is no reason to assume that bleaching occurs differently in the photoreceptors at physiological temperatures In spectroscopic investigations most of the intermediates have been detected in suspensions of rod particles after light flashes

Certain details of these reactions have an appreciable functional significance and deserve to be mentioned *Light isomerizes the retinene part of the rhodopsin molecule from the 11 cis to the all trans configuration* The 11 cis molecule *is much less stable than the all trans molecule* due to spatial overlap of the hydrogen atom on carbon atom 10 with the methyl group on carbon atom 13 In darkness and at physiological temperatures the reaction from the less stable to the more stable does not occur because the energy barrier separating the two

isomers is too high A light quantum supplies the necessary free energy and isomerization can take place

The photon probably excites the retinene molecule by raising one of the π electrons in the double bond from a bonding orbital to an anti bonding orbital Thus only a single σ bond is left and the molecule can rotate around the bond before the excited electron falls back to the bonding π orbital The excitation takes most easily place when the electric vector in the photon is parallell to the axis of the chemical bond and it does not occur when the electric vector is perpendicular to the bond

There is no change in the retinene part of the rhodopsin molecule during the dark reactions The changes take place in the opsin molecule and in the bonds between retinene and opsin Different kind of evidence indicate that the isomerization of retinene occurs without concomitant change in the conformation of opsin Of the subsequent reactions the transitions from lumirhodopsin to metarhodopsin I and from metarhodopsin I to metarhodopsin II involve great changes in the molecule with a loosening up of the protein fabric while the two other reactions seems to involve minor conformational changes

The rhodopsin molecules are not packed with random orientation along the membranes The evidence is the following Planepolarized light that strikes a rod from the side is absorbed if its electric vector is perpendicular to the long axis of the rod but not if its electric vector is along the long axis of the rod Consequently all the light absorbing groups have their axis in the membrane plane and not out of it Hagins discovered in 1955 that the light absorbing groups are free to rotate in this membrane plane A single very brief flash of plane polarized light which strikes a rod along the long axis however bright could never bleach more than about half of the rhodopsin molecules A second flash delivered within a millisecond had no bleaching effect but if the flash was delivered several tens of milliseconds later it would bleach half of the remaining rhodopsin Some of the pigment molecules had obviously rotated probably due to random thermic movements

Von Frisch showed in 1949 that bees are capable of perceiving the direction of vibration of polarized light Later many other insects crustacea and molluscs as squid and octopus are shown to have similar abilities while all vertebrate organisms which are investigated lack the ability The analyzer for the plane of vibration is not in the dioptric system but in the rhabdomeres of the sensory cells Each ommatidium of a compound eye consists of about eight sensory cells Fig 5 shows a section through one ommatidium with seven sensory cells All the tubes in the rhabdomere in each sensory cell are parallell and they are radially oriented in the ommatidium Thus if the visual pigments have the same ordered arrangement in relation to the tubes in these visual cells as they have in relation to the discs in vertebrate rods the molecular mechanism of the analysis of polarized light can be accounted for Plane polarized light which

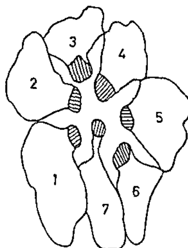


Fig 5
Transverse section through an ommatidium From von Frisch (1967)

strikes the tubes with the electric vector along the tubes can excite all pigment molecules in the membranes while plane polarized light which strikes with the electric vector perpendicular to the tubes can only excite some of the pigment molecules In the schematic drawing in Fig 6 the molecules on the top and bottom of the tubes can be excited while pigment molecules on the side of the *tubes can not Thus light with the former plane of vibration will be a more* effective stimulus to these cells

The next main step in the excitation process is the transmission of information from the pigment molecules to the regions where action potentials are produced It is widely believed that this transmission at least partly is an electrical one like that of nerve and muscle cells because photoreceptors look like neurons and because only an electrical transmission system is thought to be fast enough to account for the short latency of vision But it has been hard to get good experimental evidence for electrical transmission in photoreceptors The cells are for instance usually too small to yield good intracellular recordings of their membrane potentials and much of the evidence is still deduced from recordings of electric potentials in the extracellular spaces around photoreceptors

In all sensory cells so far studied for instance *mechanoreceptor* cells the transmission begins with flow of transmembrane current near the point where a signal originates (Fig 7a) This initial current is called the receptorcurrent A common hypothesis is that the passive spread of this initial current along the *cell cytoplasm* and out through its membrane effects the flow of information from the current source to regions where action potentials are produced The



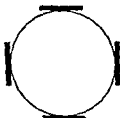


Fig 6
Schematic drawing of one of the membrane tubes in an arthropod rhabdomere The bars represent the light absorbing axis ir the pigment molecules The arrow represents a photon with the plane of polarization in the paper plane

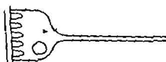






Fig 7
Schematic drawing of three different receptor cells and the current gen rated by the stimulus

current out through the cell membrane in the region where the action potentials originate is called the "generator current because it generates nerve impulses

According to this hypothesis the receptor current crosses the cell membrane in the photoreceptors near the pigment bearing structures This does not mean that the *receptor current must cross the membrane precisely where a photopigment molecule is excited* because it is possible for other space spanning mechanisms to intervene between the photochemical events and the production of the *receptor current* Thus *we have at least two possible mechanisms Either the* absorbed photon makes the cell membrane locally permeable to an ion whose inward flux is narrowly concentrated around the light absorbing molecule or one photon might release a number of transmitter molecules which diffuse before reaching the cell membrane and increasing its ionic permeability

While the experimental observations from invertebrate photoreceptors fit this general model rather nicely (Fig 7b) experiments on vertebrate retinas give some unexpected results (Fig 7c)

The currents in the squid retina have been thoroughly investigated by extracellular recordings by Hagins (Fig 7b) He found that the response to one photon consists of an inward positive membrane current lasting less than one tenth of a second and entirely confined to a region within 7 μ of the absorbing pigment molecule 7 μ is a small distance compared to these rhabdomers which are about 250 μ long The total charge which flows often exceeds 10^3 electronic charges The current flows along the cytoplasm of the cell depolarizes the membrane emerges through it over a wide region and returns to the absorbtion site in the interstitial spaces of the retina There is also good evidence that the current enters the receptor cells as sodium ions Partial reduction of the sodium concentration in the sea water bathing the retina by substitution by choline reduces the receptor current proportionately It was not necessary to postulate any catalytic mechanism or chemical amplification in the rhabdomers of the photoreceptors to account for their ability to count single photons The radius of a hypothetical hole" in the membrane would only have to be of the order of molecular dimension to give the observed current Thus the energy for the amplification might simply be supplied by the sodium pump as it is in the conduction of nerve impulses

The first intracellular recordings from photoreceptors where made in 1952 in the lateral eye of Limulus by Hartline Wagner and MacNichol and the intracellular response of the eccentric cell in these eyes has later been investigated in detail especially by Fuortes The response of these cells to illumination was a depolarization with superimposed spikes In steady state conditions both the amplitude of the generator potential and the frequency of firing are approximately linear functions of the logarithm of light intensity The generator potential seems to be caused by ionic currents through the cell membrane again with sodium as the most important ion However the anatomy and physiology

of the lateral eye of Limulus is not typical for a compound eye There is strong electric and chemical coupling between the sensory cells in each ommatidium. In other arthropods for instance in the ordinary house fly and in the locust the eight sensory cells are independent

Recently Smith et al have found a mechanism of receptor potential generation in the ventral eye of Limulus that differs remarkably from the current passive diffusion explanations Their hypothesis is that the photoreceptors have an electrogenic sodium pump which contributes directly to the steady state membrane potential in these cells and which is the current generator altered by light

Under dim illumination and when the spike mechanism is blocked, the generator potential in the locust eye resolves into trains of irregular quantized voltage fluctuations (Fig 8) These fluctuations resemble synaptic potentials the frequency increases linearly with light intensity and they are Poisson distributed in time The suggests that each fluctuation is generated by one photon. In the dark adapted house fly Reichardt has shown that each photon generates one spike

Let us for a moment return to the problem of perception of polarized light The individual cells in an ommatidium in the light adapted house fly respond

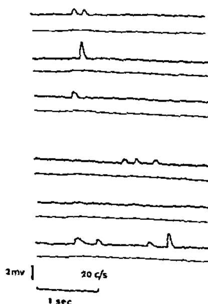


Fig 8
Generator potentials recorded from a locust eye during low illumination
From Scholes (1965)

with generator potentials of different amplitudes to polarized light of differing planes of vibration Rotating the polarizer maxima and minima are obtained for every shift of 90°, as expected The spike frequencies in the axons show similar cyclic variations

The *electrical response to light in vertebrate retinas* was discovered by Holmgren in 1865 and has later been studied extensively by Granit The ordinary electroretinogram is obtained with one electrode on the cornea and the other somewhere else in the organism The upper part of Fig 9 shows an idealized local electroretinogram recorded with the second electrode inserted into the retina On exposing the eye to a flash of light there is a biphasic fluctuation of potential first a cornea negative component the a wave then a cornea positive component the b wave Because of the short latency Adrian and Matthews assumed the a wave of the electroretinogram to orginate in the receptors themselves The maximum amplitude of the a wave was found by Brown near the outer segment of the receptors It was concluded that the a wave is the leading edge of a component generated by the receptors The b wave was found to be generated by cells of the inner nuclear layer The receptor component is now referred to as the late receptor potentilal since an early receptor potential has also been found The late receptor potential is apparently generated by ordinary ionic mechanisms since the a wave is reduced by either excess extracellular potassium or lowered extracellular sodium The amplitudes of the late re*ceptor potentials are approximately linear with the logaritm of stimulus inten*sity

The potential gradient of the late receptor potential along the photoreceptor shows that during the response there is extracellular current flow from the region of the outer segments towards the axon terminals (Fig 7c) It should be

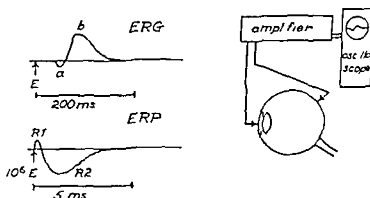


Fig 9
Idealized drawing of the late and early receptor potentials from the vertebrate retina
From Wald (1968)

emphasized that this direction of the extracellular current flow is opposite to that found in invertebrate photoreceptors and in other sensory cells Tomita has recently made intracellular recordings from gold fish cones (Fig 10) The receptor potentials were always hyperpolarizing and thus in agreement with the extracellular recordings

Spikes have not been observed in vertebrate photoreceptors Some unknown transducer mechanism must obviously intervene between this hyperpolarizing receptor potential and the production of spikes in either the bipolar or the ganglion cells of the retina However the physiology of the bipolar cells and the relevant synapses is virtually unknown It is not even known whether information is carried through the bipolar cells as spikes or as graded potentials although the evidence seems to indicate that the bipolar cells only produce hyperpolarizing or depolarizing graded potentials as described by Kaneko and Hashimoto Spikes are of course generated in the ganglion cells

About six years ago Brown and Watanabe described a still earlier potential than the a wave in the vertebrate retina with a latency of 25 μs or less (Fig 9) This early receptor potential is also biphasic consisting of a rapid cornea positiv wave called R1 followed by a slow cornea negativ wave called R2 Both phases of the early receptor potential have maximum amplitudes in the receptor layer in the retina and the action spectrum follows closely the absorbtion spectrum of rhodopsin From this and other evidence it seems established that both phases of the early receptor potential is generated by the photoreceptors and both phases result from the action of light upon visual pigments

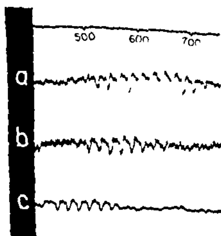


Fig 10
Receptor potentials recorded from gold fish cones From Tomita (1965)

There are strong indications that the early receptor potential is generated in a fundamentally different manner from the electrical responses of nerve cells First it shows a high resistance to anoxia Second the early receptor potential is unchanged during strong depolarization of the receptor for instance by high extracellular potassium concentration Third the initial peak of the early receptor potential has been recorded at $-35°$ C from frozen eyes The second peak is almost completely abolished at 0° C These results suggest that the two peaks are produced by independent processes And that the early phase still persists in frozen eyes argues that it is generated not by the moving about of molecules but rather by a charge in the molecules themselves — say the establishment of dipoles by conformational *changes in molecules If the molecules are oriented* in relation to the electrodes the individual dipole fields could sum and yield an experimentally observable potential The contribution per pigment molecule is so small that about 10^5 pigment molecules per rod must be excited for this response to be experimentally observed and the amplitudes are proportional to *the number of pigment molecules excited in the experimental range Thus* the amplitudes probably do not exceed a few nanovolts when a rod is excited by a single photon Apparently the late logaritmic receptor potential is an amplified response but the early linear receptor potential is not

At which point in the bleaching of rhodopsin (Fig 4) is the information *transmitting* electrical signal generated? *It has been clear for many years that* the late receptor potential must be generated prior to the relatively slow hydro lysis of metarhodopsin II All reactions up to and including the formation of metarhodopsin II must therefore be considered as possible sources of excitation The early receptor potential has not yet been demonstrated to be in the direct pathway of excitation *However* as a useful *working hypothesis we may* consider the possibility that the early receptor potential in some manners trigger the late receptor potential for instance by opening up ionic channels in the *membranes Since the initial peak of the early receptor potential has been re* corded down to about -35 C it must be generated during or prior to the formation of metarhodopsin *I which is stable at this temperature Finally* the strong temperature dependence of the time from the onset of stimulus to the top of the positive peak strongly suggests that the positive peak not is produced in the initial photochemical step Thus the critical steps appear to be either the step going from prelumirhodopsin to lumirhodopsin or the step in which lumir *hodopsin is transformed to metarhodopsin I If the early receptor* potential is a result of conformational changes in the pigment molecules with formation of dipoles the main interest is focused on the last of these two reactions The first of these reactions is accompanied by only small conformational changes while the conformational changes are great during the last reaction Recent investiga *tions by Falk and Fatt on* the electrical properties of outer segments from rods in suspensions support these ideas

The potential must be amplified considerably in order to convert the effects of one photon on a single molecule of rhodop in into the late receptor potential Hagins has shown that local permeability changes in the membrane may be sufficient to be responsible for this amplification while Wald has suggested an intervening enzyme chain with multiplied turnover similar to blood clotting to explain the amplification At present very little experimental evidence is directly in favour of any of these hypotheses

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perimeter (1945) may be obtained also in arc perimeters by transmitting light from the projection lamp to the arc through a glass fibre light guide The free end of the light guide ideally placed on the midpoint perpendicular to the arc can be shaped so as to distribute the transmitted light with high efficiency Such a device is small in bulk and may be installed with minor modifications of the perimeter It is easily screened so as to remain invisible to the subject at all positions of the arc The heat emission is negligible

Although the following description applies primarily to the Zeiss Maggiore perimeter it is easily adapted to other makes The dimensions given below are not critical

Materials and Methods

Fibre optics One 24 length of flexible light guide with a diameter of ¹/₈ (LGM 5 24 American Optical Company Southbridge Mass) was used One of the stainless steel end tips was removed by electrolysis in a solution of iron chloride The freed fibre bundle was then locked between the two halves of an aluminium cylinder The outer end of the central bore was widened to a funnel like cavity (Fig 1) the dimensions of which are determined by the minimum radius of bend of the glass fibres (³/₈) and the desired direction of the trans mitted light rays (in this case 67° from the cylinder axis) The epoxy cement holding the 6 000 individual strands of clad glass together was softened by im mersion in chloroform Some 50 fibres at a time were then carefully bent and

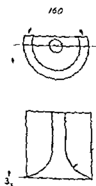


Fig 1
The split cylinder serving as support for the glass fibres The screws fixing the smaller back plate to the larger arc facing part are not shown

From the Department of Anatomy Faculty of Medicine University of Goteborg Sweden

INTEGRAL ARC ILLUMINATION FOR PROJECTION PERIMETERS

BY

L FRISÉN

The importance of securing uniform and constant illumination of the back ground in studies of the visual fields is well known The deficiences of daylight or spotlight illumination of a perimetric arc or bowl are also well recognized *(Lauber* 1944 *Smith* 1962) The goal can only be achieved by means of arti ficial illumination from a suitably located built in light source Hemispherical perimeters are ideally illuminated according to the principle introduced by *Goldmann* (1945) while the more common arc perimeters with varying success may use one of the following positions of the light source

i on the midpoint perpendicular to the arc *(Ferree & Rand* 1922)
ii at one end of the arc *(Traquair* see *Scott* 1957) or
iii along the arc *(Harrington* 1964)

Only the first arrangement is commonly used since it will supply a reason ably even illumination at the same time as it is little disturbing to the subject and his examiner Yet the midpoint localization suffers from the drawbacks that the subject may perceive the lamp directly at certain positions of the arc and he may be bothered by its heat

In projection perimeters where a light spot projected on the background re places reflecting objects one and the same lamp should serve as light source for both light spot and background since the perpetual fluctuations in power supply will affect the luminous fluxes of two lamps differently The brightness con trast between light spot and background is best kept constant by using a single light source Such integral illumination elegantly utilized in Goldmann s bowl

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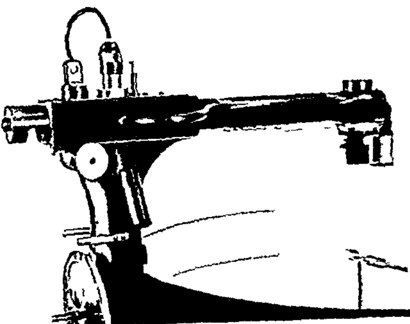


Fig 3
The gl s fibre light guide installed on the Zeiss Maggiore perimeter

were no measurable or perceptible differences in illumination of different parts of the arc

Comment

This simple device will give an even illumination of a magnitude that permits control of the subject s fixation and handling of the perimeter Though considerably smaller than the degree of illumination recommended for use with reflecting test objects (1 5 foot candles = 80 lux see *Lauber* 1944) it still lies within the rang recommended by *Goldmann* (1945) and above the lower limit of photopic vision The colour and the intensity of the transmitted light may be varied by introducing suitable filters in front of the housing end of the guide The transmiss on is approximately constant throughout the wavelength range of photopic vision

The main advantage of this arrangement is that fluctuations in power supply and decreasing light output with increasing age of the lamp will not affect the

cemented to the funnel walls by means of Eastman 910 Adhesive (Eastman Chemical Products Inc Kingsport Tennessee) taking care to distribute the fibres evenly over the funnel wall Every third layer of fibres was coated with a thin film of epoxy cement (Araldit®, Ciba A G Basel), taking care not to contaminate the polished fibre ends (Fig 2) A lucite cap was finally slipped on the cylinder to protect the fragile glass fibres The base of the cap was painted matte black

Mounting The original light source of the projection system was used to feed the light guide The light was condensed by means of a concave glass mirror (f = 12 mm) placed at one side of the lamp The position of the mirror was adjusted so as to give a maximum of light to the unretouched end of the light guide which was fixed to the housing on the opposite side of the lamp The mirror was held in place by means of an aluminium sheet pressed into place in the housing This arrangement did not interfere with the projection of the stimulus light spot nor with the optical eye aligning system or the chart illuminating mirror

The aluminium housed end of the light guide was screwed to the arm carrying the revolving mirror as close to the mirror as possible (Fig 3) The guide itself was strapped to the arm

With the standard light source of the Zeiss perimeter (15 watts) the background will receive about 20 lux (2 foot candles) while a similar 30 watts lamp supplied about 45 lux as measured with a Gossen Lunasix lightmeter There



Fig 2
The rearranged fibre bundles and the aluminium cylinder

ACTA OPHTHALMOLOGICA VOL. 47 1969

From the University Eye Clinic Lund
(Head Professor Erik Palm)

ANTIGLAUCOMATOUS SCLERECTOMY

A follow up of 25 operated eyes

BY

ARVID ANSETH and BERTIL LINDER

In an earlier report (*Anseth & Linder* 1965) the surgical technique and the preliminary results obtained by sclerectomy in 25 eyes were reported The results were promising but the observation time was short only between 4 and 19 months It therefore seemed to be of interest to find out if the results were reliable for a longer period of observation

Results and Discussion

Table 1 shows the results of the operation The observation time is between 16 and 72 months The table includes 19 cases of *glaucoma simplex* (gl simpl) 4 cases of *glaucoma postiritidem* (gl irit) one case of *glaucoma pigmentosum* (gl pigm) and one case of *glaucoma post traumaticum* (gl. traum) The post operative intraocular pressure (I P) was normalized (20 mm Hg) without therapy in 9 cases of gl simp (cases 1 9) in one case of gl irit (case 20) and in one case of gl pigm (case 24) In 8 *cases of gl* simpl (cases 10 17) and 2 cases of gl irit (cases 21 22) the I P was normalized with local antiglaucomatous therapy In 2 cases of gl simpl (cases 18 19) in one case of gl irit (case 23) and in the only case of gl traum (case 25) the I P was not normalized Two

Received April 4th 1969

brightness contrast between light spot and background Once installed the device does not require control or maintenance

Summary

A fibre optic arrangement for the uniform illumination of the arc of projection perimeters is described By transmitting light from the projection lamp to the arc the brightness contrast between the projected light spot and the background is made independent of variations in luminous flux The necessary perimeter modifications are minor

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Table [illegible]

No	Age and Sex	Diagnos	Postop Compl: Hyp haema	Postop Compl: Flat ant chamber	Reop	I P normalized ≦ 20 mm Hg: without local therapy	I P normalized ≦ 20 mm Hg: with local therapy	I P not normalized	Vision: unchanged	Vision: reduced	Visual field: unchanged	Visual field: reduced	Obs time in months	Comments
1	60 F	Glaucoma simplex				+			+		+		68	Subnormal I P
2	55 M	Glaucoma simplex				+			+		+		6[illegible]	Subnormal I P
3	64 M	Glaucoma simplex		+		+				+	+		65	Senile cataract explains vision
4	[illegible]2 F	Glaucoma simplex		+		+			+		+		63	
5	6[illegible] F	Glaucoma simplex				+			+		+		60	
6	62 F	Glaucoma simplex				+				+	?		60	Subnormal I P – Cataract
7	59 M	Glaucoma simplex				+			+		+		58	
8	[illegible]0 F	Glaucoma simplex		+		+			+		+		24	
9	[illegible]1 M	Glaucoma simplex	+		+	+				+	+		28	Senile cataract explains vision
10	62 M	Glaucoma simplex		+			+		+		+		[illegible]6	
11	[illegible]0 F	Glaucoma simplex		+			+			+	+		[illegible]	Senile cataract explains vision

13	71 M	Glaucoma simplex		+			+			+		+	61	Highly reduced visual field praeop
14	52 F	Glaucoma simplex		+			+		+		+		60	
15	66 M	Glaucoma simplex			+		+		+		+		44	Peop after 2½ years
16	59 M	Glaucoma simplex			+		+			+		?	17	Highly reduced visual field praeop
17	59 M	Glaucoma simplex		+			+		+		+		16	
18	60 M	Glaucoma simplex	+					+	+		+		72	I P = 23 mm Hg
19	67 M	Glaucoma simplex	+					+	+		+		45	I P = 23 mm Hg
20	61 M	Glaucoma post iritidem				+				+	+		39	Senile cataract explains vision
21	29 F	Glaucoma post iritidem	+				+		+		+		63	Still's disease
22	59 F	Glaucoma post iritidem					+		+		+		62	
23	53 F	Glaucoma post iritidem			+ ×2			+		+	+		48	Prolaps of the ciliary body in the wound
24	71 F	Glaucoma pigmentosum				+				+	+		72	Subnormal I P – Cataract
25	33 F	Glaucoma post traumaticum			+			+		+		+	60	

Table 1

No	Age and Sex	Diagnos	Postop Compl		Reop	I P normalized ≤ 20 mm Hg		I P not normalized	Vision		Visual field		Obs	Comments
			Hyphaema	Flat ant chamber		without local therapy	with local therapy		unchanged	reduced	unchanged	reduced	time in months	
1	60 F	Glaucoma simplex				+			+		+		68	Subnormal I P
2	55 M	Glaucoma simplex				+			+		+		65	Subnormal I P
3	61 M	Glaucoma simplex		+		+				+	+		65	Senile cataract explains vision
4	72 F	Glaucoma simplex		+		+			+		+		63	
5	62 F	Glaucoma simplex				+			+		+		60	
6	62 F	Glaucoma simplex				+				+	?		60	Subnormal I P – Cataract
7	[illegible] M	Glaucoma simplex				+			+		+		58	
8	[illegible] F	Glaucoma simplex		+		+			+		+		24	
9	[illegible] M	Glaucoma simplex	+		+	+				+	+		28	Senile cataract explains vision
10	[illegible] M	Glaucoma simplex		+			+		+		+		66	
11	[illegible] F	Glaucoma simplex		+			+			+	+		[illegible]	Senile cataract explains vision
[illegible]	[illegible] M	[illegible]	+	+			+		+		+		[illegible]	

13	?1 M	Glaucoma simplex		+						+		+	61	Highly reduced visual field praeop
14	57 F	Glaucoma simplex		+			+		+		+		60	
15	66 M	Glaucoma simplex			+		+		+		+		44	Reop after 2½ years
16	59 M	Glaucoma simplex			+		+			+		?	17	Highly reduced visual field praeop
17	59 M	Glaucoma simplex		+			+		+		+		16	
18	66 M	Glaucoma simplex	+					+	+		+		72	I P = ?8 mm Hg
19	67 M	Glaucoma simplex	+					+	+		+		45	I P = 28 mm Hg
20	61 M	Glaucoma post iritidem				+				+	+		39	Senile cataract explains vision
21	?? F	Glaucoma post iritidem	+				+		+		+		68	Still's disease
22	5? F	Glaucoma post iritidem					+		+		+		62	
23	53 F	Glaucoma post iritidem			+ ×2			+		+	+		48	Prolaps of the ciliary body in the wound
24	71 F	Glaucoma pigmentosum				+				+	+		72	Subnormal I P – Cataract
25	33 F	Glaucoma post traumaticum			+			+		+		+	60	

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No	Age and Sex	Diagnos	Postop Compl		Reop	I P normalized ≦ 20 mm Hg		I P not normalized	Vision		Visual field		Obs time in months	Comments
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3	61 M	Glaucoma simplex		+		+				+	+		65	Senile cataract explains vision
4	72 F	Glaucoma simplex		+		+			+		+		63	
5	6? F	Glaucoma simplex				+			+		+		60	
6	6? F	Glaucoma simplex				+				+	?		60	Subnormal I P – Cataract
7	?9 M	Glaucoma simplex				+			+		+		58	
8	?0 F	Glaucoma simplex		+		+			+		+		24	
9	?1 M	Glaucoma simplex	+		+	+				+	+		28	Senile cataract explains vision
10	62 M	Glaucoma simplex		+			+		+		+		66	
11	70 F	Glaucoma simplex		+			+			+	+		?0	Senile cataract explains vision
[illegible]	?7 M	[illegible]	+	+			+		+		+		?2	[illegible]

favourable results of filtering operations for the time being speaks in favour of a more conservative treatment of glaucoma

Reference

Anseth A & Linder B Antiglaucomatous sclerectomy A preliminary report. Acta Ophth 1965 *43* 281

of these cases (cases 18-19) *with a slight increase in I P* showed no reduction of visual acuity or visual field during the observation time

Reduction of visual acuity was observed in 10 eyes (cases 3 6 9 11 13 16 20 23 24 25) *and reduction in visual field in 3 eyes* (cases *13 16 25) In 4* cases the cause of the reduction in vision was increasing senile cataract Reoperation was performed in 5 eyes (cases 9 15 16 23 25) the second operation *being successful in 3 of them*

Postoperative subnormal I P was noticed in 4 eyes (cases 1 2 6 24) and in 2 of these a complicating cataract developed

In table 2 a comparison *is made between the results obtained after a short* and after a long observation time A prolongation of the observation time decreases the number of successful cases with normalized I P without therapy

The material presented in this paper is carefully examined and followed from the day of surgery As would be expected postoperative complications as hyphaema and flat chamber sooner or later usually lead to less favourable results (table 1) Table 2 clearly demonstrates the importance of following the operated cases for a longer period of time to be able to *draw any conclusions* about the result of the operation This statement is also valid for other antiglaucomatous filtering operations It is a close relationship between relatively minor postoperative complications and less favourable results *This makes a careful selection* of cases suitable for antiglaucomatous filtering operations important. During the last years an increasing number of effective remedies for conservative treatment of glaucoma has been available This *fact together with the relatively* un

Table 2

	I P normalized		I P not normalized	Vision		Visual field	
	without therapy	with therapy		un changed	reduced	un changed	reduced
Short observation time	19	5	1	22	3	25	0
Long observation time	11	10	4	15	10*	22	3

* 4 of these because of senile cataract

favourabl results of filtering operations for the time being speaks in favour of a more conservative treatment of glaucoma

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From the Department of Ophthalmology (Head Prof A Huggert)
University of Goteborg Sweden

STUDIES WITH IMPEDANCE CYCLOGRAPHY ON HUMAN OCULAR ACCOMMODATION AT DIFFERENT AGES

BY

GUNNAR SWEGMARK

In a previous paper (*Swegmark & Olsson* 1968) a new method for the recording of accommodation was presented This method impedance cyclography (ICG) was shown to reflect ciliary muscle activity

This possibility of recording what has been called the physiological accommodation leads to some interesting applications in the study of accommodation and its relation to presbyopia There is evidence that lenticular sclerosis plays a major role in the continuous impairment of accommodative ability with increasing age but the possibility that a decrease in the function of the ciliary muscle might be a contributing factor has been pointed out rather recently by *Teramoto* (1959) A related problem presenting more conflicting evidence is the question of whether the same activity of the ciliary muscle is required to produce a unit change of refraction at all ages or if in older subjects more muscular activity is required than in young ones The first mentioned view has been stressed by *Gullstrand* (1909) and the latter by *Donders* (1866) The evidence which can be put forward to support one or the other theory was recently reviewed by *Alpern* (1962) who pointed out that it is still too early to make a decisive choice between these two antagonistic views of presbyopia

The aim of the present study was to investigate the ciliary muscle activity

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during accommodation at different ages using the method of impedance cyclography (ICG)

Material and Methods

Patients from the Outpatient Department of the Eye Clinic of the Sahlgrenska sjukhuset Goteborg Sweden and a few members of the staff at the clinic were included in this study All subjects were free from relevant ocular abnormalities had at least 20/20 vision and a refraction of each eye ranging between −0 75 and + 1 0 diopters A few cases of astigmatism amounting to maximally 0 75 diopters were included The patients had consulted the outpatient department because of minor ailments viz superficial foreign bodies hyposphagma lacrimal obstruction Twenty four volunteers were selected for the experiments Four of these had to be rejected because of their inability to cooperate adequately From the remaining 20 subjects recordings suitable for analysis were obtained Some relevant data about these subjects are presented in Table I In this table the subjects are arranged and numbered in order of age and will be referred to by these numbers in the text

Equipment The impedance recording equipment was presented in detail in a previous communication and in this context the measuring principle will only be briefly outlined here

Four platinum disc electrodes were mounted on a suction cup so that they were pressed against the perilimbal ocular surface A constant 50 kHz current was fed through one pair of diametrically placed driving electrodes The voltage drop caused by the tissue was measured by means of a pair of sensing" electrodes As the strength of current was held constant any changes in voltage depended upon impedance changes between the sensing electrodes

During alterations in fixation distance impedance changes resulting from ciliary muscle activity could be recorded

The electro oculographic (EOG) recordings of vergence movements in some experiments were performed using Beckman® Miniature Skin Electrodes instead of the silver EEG electrodes described in the previous paper otherwise the equipment for recording ocular movement was the same as that used previously

The device used for presenting fixation stimuli was the same as that described in the previous paper with a few modifications Two targets were used one at a fixed distance of 200 cm from the test eye (from which the cyclogram was recorded) the other at a distance from the corneal surface that could be varied between 70 and 8 cm (Fig 1) The targets consisted of crosses that were illuminated by small electric bulbs in the manner described in the previous

Table I

Subject No	Age years	Sex	Refraction diopters		Amplitude of acc diopters	
			Test eye	Opposite eye	Test eye	Binocular
1	22	M	0	0	6 0	6 8
2	23	M	+ 0 5	+ 0 5	7 6	9 5
3	24	M	+ 0 25	+ 0 5	7 9	8 0
4	32	M	− 0 5	− 0 25sph−0 75c0°	6 1	6 3
5	34	F	− 0 5c165°	− 0 25sph−0 5c20°	5 6	
6	35	M	− 0 75	− 0 75	6 2	6 9
7	37	M	+ 0 25	+ 0 25	6 4	7 1
8	46	M	+ 0 25	+ 0 5	1 9	2 5
9	47	M	+ 0 5	0	2 8	2 6
10	47	F	+ 1 0	+ 0 75	1 6	1 2
11	48	F	0	0	1 3	1 5
12	49	M	− 0 5	− 0 25	1 3	1 5
13	50	F	+ 0 5	+ 0 25	0 3	0 7
14	54	M	0	0	3 3	3 3
15	54	M	+ 0 5sph−0 5c140°	+ 0 25sph−0 5c20°	2 1	2 0
16	58	F	+ 0 75sph−0 5c90°	+ 0 25	0 2	0 2
17	59	M	+ 0 25	+ 0 5sph−0 5c65°	0 3	1 2
18	61	M	+ 0 5	+ 0 5	0 8	1 6
19	62	M	+ 0 5	0	0 8	0 9
20	68	M	+ 0 5	+ 0 5	0 3	0 4

paper In the present study the illumination was changed from one fixation target to another with an electronic microswitch that could instantaneously change the current from one bulb to the other The illumination of the near target was picked up by a photocell and recorded on a Mingograf 34 Recorder (Elema Schönander A B Stockholm) The stimulus was thus recorded simultaneously with the cyclographic and electro oculographic recordings The photocell was arranged so that an increase in illumination was recorded as the near target was brought closer to the eye In this way both the duration and the amplitude of the near stimulus was recorded

The fixation targets were presented against a background consisting of a wall covered with black cloth The distant target was attached to the wall and at the same height there were six small openings in the cloth three on either side Each of them could be illuminated from behind by a small electric bulb Their distance from the central target corresponded to an angle of 10 20 and 30 degrees respectively as viewed by the subject These bulbs were used for the calibration of the electro oculographic recording

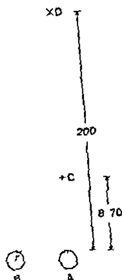


Fig 1
Experimental arrangement during binocular experiments The ICG is recorded from the test eye (A) which looks alternately at the two fixation targets C and D The movements of the opposite eye (B) are recorded by means of EOG Distances in cm.

Procedure The refraction of each eye was measured to the nearest 0 25 diopters by the method of Donders at a distance of 5 m The amplitude of accommodation was determined first in each eye separately and then binocularly by means of a push up test of small print. The subject was instructed to indicate when he could no longer clearly read the text when this was slowly brought closer to the eye starting from a distance of 30 cm With the older subjects it was necessary to use a positive spectacle correction during this test The near point measurement was done to the nearest 0 5 diopters and repeated three times with each eye and binocularly The amplitude of accommodation was then calculated from the mean value of the three measurements after correction for refraction and the additional lenses that were used *in some cases* during the test

The subject was thereafter seated in the dimly lit laboratory After cleansing of the skin with 70 % ethanol the EOG electrodes were placed at the lateral and medial canthus of one eye and on the lobe of the ipsilateral ear

The other eye (the test eye) was anaesthetised with 1 2 drops of 0 4 % benoxinate (Novesine® Wander) and a suction cup with four ICG electrodes was tightly fixed to the eye using a vacuum of 30 mm Hg

The subject was then seated with his head in a chin and forehead supporting stand that was adjusted so that the two fixation targets were seen along the

line of sight of the thest eye (Fig 1) The subject was instructed to keep his head steady during the experiment

The two fixation targets were presented alternatingly a few times with the near target at a distance of 16 7 cm from the anterior corneal surface of the test eye Any correction for the individual refraction was not made and therefore in the following text a 2 diopter" stimulus indicates a target distance of 50 cm a "4 diopter" stimulus means 25 cm and so on The amplification of the eye movement (EOG) and ICG recordings were adjusted to a suitable level That the head was steady during the experiment was controlled by making sure that no difference could be observed in the direction of gaze of the test eye during the changes in fixation distance

The ICG curve was adjusted to a neutral level during distant fixation The potentiometer setting then corresponded to the basal level of impedance be tween the two sensing electrodes This measurement was made with the usual four electrode mode and in most cases (by short circuiting the electrodes pair wise) also with a two electrode mode The value read off during the two electrode measurement included the contact impedance with four electrode measurement the contact impedance was eliminated and only the tissue impe dance was measured The difference between these two values then correspond ed to the contact impedance of each electrode

The ICG curve was calibrated by pressing a button producing a 2 ohm deflection in the recording

The EOG recording of eye movements from the opposite eye was calibrated by letting the subject look binocularly at the distant target alternating with one of the small electric bulbs at 10 20 and 30 degrees distance in the direction of convergence of the eye in question

The experiment was then started by letting the subject look binocularly at the far target until the recording showed a steady level The subject was told to fixate on the center of the target illuminated at the moment The illumina tion was changed over to the near target for a period of 3 6 seconds and then back to the distant target Each target was observed twice When occasional inattendance of the subject gave rise to obviously irregular and not analyzable curves the near target was presented more than twice The distance to the near target was then altered As this study deals with the impedance deviations cor responding to different changes in fixation distances it was not considered necessary to vary the near stimulus in a random fashion as this might confuse the subject and provoke irregular recordings Instead the stimulus was altered in a regular manner in steps of 2 diopters To compensate for a possible in fluence of the direction of change the near target was usually presented in the order 6 8 10 8 6 4 2 4 diopters and this sequence was repeated one or several times depending upon the cooperability of the subject In experiments with monocular stimulation the opposite eye was occluded

During the experiment the electro oculographic calibration was repeated at intervals of about 5 minutes At the end of the experiment the ICG recording was recalibrated and the basal impedance measurement was repeated

Most subjects were examined on two separate occasions on different days The results from the day on which the most complete set of measurable responses was obtained were used in this study which usually meant that in these cases the results from the first day were eliminated The sign test was applied to the individual mean responses during binocular vision on two different days in 13 subjects No significant systematic difference was found between the magnitude of the eye movement or ICG responses on the first and the second day of investigation ($p > 0.05$)

Calculations As a measure of the degree of contraction of the ciliary muscle the amplitudes of the deviations of the ICG curve during changes of fixation distance were calculated from the recordings This was done by measuring the difference between the impedance levels during distant and near fixation (Fig 9) In the following text this value will be referred to as the ICG amplitude In some trials no steady level was reached during near fixation and these deviations were not measured The same applies to occasional irregular curves and obvious cases of inattendance of the subject The amplitude measurements in millimeters were then transformed to ohms by means of the 2 ohm calibration The mean value of at least 5 consecutive calibrations was used

The speed of contraction and relaxation of the ciliary muscle during accommodation was also considered interesting as an aspect of the function of the muscle For this purpose the maximum slope of the ICG curve during changes of fixation distance was measured both during far to near and near to far changes This was only made on curves free from notches and irregularities During near to far changes with binocular fixation movement artifacts sometimes made the curves unsuitable for this kind of analysis The measurement

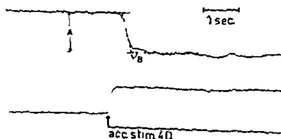


Fig 9
Measurement of ICG amplitude (A) and velocity (B) from the recording

was made by fitting a tangent to the curve at its steepest part and measuring the slope of this line (Fig 2) The slope was expressed in ohms per second

The electro oculographic recording was measured in the same manner as the ICG but only amplitude measurements were made The measures were transformed to degrees by means of the 10 20 and 30 degrees calibration made on different occasions during the experiment A straight calibration line was drawn based upon all the changes of gaze included in the calibrations during the experiment In almost every case the approximation to linearity was good *However occasional slow changes in the corneo retinal potential resulted in* differences in the deviations for a unit change of gaze at different times during the experiment In a few cases these differences were so large that the eye movement recordings could not be used except immediately after a calibration In the accepted recordings the mean EOG changes during a certain eye move*ment stimulus at a certain calibration did not differ more than ± 10 % from* the calibration line

Statistical methods Current statistical methods were used (see for example *Dixon & Massey* 1957) In order to test the association between age and certain variables the rank correlation coefficient was computed A 5 % level of significance was used in the statistical testing of hypotheses The significant characteristics in the tables are marked with an asterisk

Statistical symbols

$\bar{X}$ = arithmetic mean
$s_{\bar{x}}$ = standard error of the mean
N = number of observations
r = product moment correlation coefficient
r_s = rank correlation coefficient

Results

The data for refraction and accommodation amplitude are given in Table I The mean basal ocular impedance was 81 4 ± 2 47 ohms ($\bar{X} \pm s_{\bar{x}}$ N = 20) and the electrode tissue contact impedance 305 1 ± 8 41 ohms (N = 16) None of these measures was significantly correlated to age (r = − 0 059 and + 0 186)

Monocular vision

An accommodation stimulus with monocular fixation was presented to all subjects *In most cases a far to near change of fixation distance during monocular*

* Advice on statistical matters was provided by Marianne Frisén B A

fixation was accompanied by a decrease in the impedance of the test eye (Fig 2) and a convergence movement of the occluded eye

Fig 3 shows some examples of the relationship between stimulus and response found in these experiments The lines were fitted by the eye and indicate the general tendency of distribution of the values Fig 3 a shows a rather common type of relationship At low and moderate stimulus levels there is an increased response with increased stimulus but at higher stimulus levels the response does not increase but may instead decrease This type of curve was found in cases number 1 2 3 8 9 10 and 14 In some cases however there seemed to be a rising tendency within the whole stimulus interval studied Such an example is shown in Fig 3 b This type of relationship with approximate linearity or a more or less obvious upward convexity was found in cases 4 5 6 7 and 1? In each subject the type of stimulus response relationship was similar for the eye movement and ICG curves so that almost constantly the fitted lines corresponding to these two kinds of responses ran more or less parallel as is seen in Fig 3 This suggests a strong correlation between ICG amplitude and accommodative convergence Fig 4 shows this relationship and is based upon the data of Fig 3 In both subjects a fair approximation to linearity can be observed For descriptive purposes a straight line was fitted to the data by the method of least squares No attempt was made to test the linearity of the relationship The method of least squares is not suitable for testing the linearity of a relationship between accommodation response and accommodative convergence which are both dependent variables subject to errors of measurement

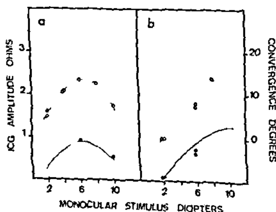


Fig 3

Stimulus response relationship during monocular vision in two subjects Diagrams a and b refer to subjects number 9 and 7 The open circles represent convergence and the filled circles ICG amplitude

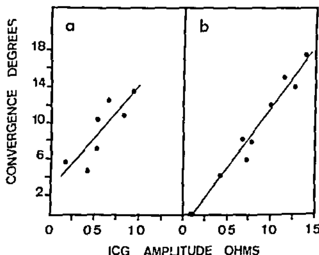


Fig 4

Relationship between ICG amplitude and accommodative convergence during mono cular vision The diagrams are based upon the data of Fig 3

However to summarize the information in Fig 4 this method was considered useful The relationship between accommodative convergence and ICG amplitude can then be characterized by the slope of the fitted line corresponding to the regression coefficient (b) As a measure of the dispersion of the values around the line the correlation coefficient (r") was calculated Table II shows these two characteristics in the 13 cases where monocular stimulation gave analyzable responses As can be seen the correlation coefficient has a high value ranging between 0 84 and 0 99 with the exception of case number 1 This means that the fitted line describes the distribution of the measured values fairly well in almost every case

With some subjects monocular stimulation did not result in any appreciable response in the ICG or EOG recording This applies to subjects 11 13 15 16 17 19 and 20 that is mainly the older subjects In subject 18 the stimulus response relationship was not easily characterizable owing to the large variability of the responses However in this case also an approximately linear relationship was found between accommodative convergence and ICC amplitude

The rank correlation coefficient in table II shows no significant correlation between age and b value

Binocular vision

A binocular stimulus to near vision involves a stimulus to accommodation but also a fusion stimulus With this more complicated situation it is to be expected that the responses of accommodation and convergence will be different from

Table II

Relationship between ICG amplitude and accommodative convergence during mono cular vision b is the regression coefficient for the line fitted to the data by the least squares method and r is the product moment correlation coefficient for these data r_s is the rank correlation coefficient between age and b

Subject number	Age years	b degrees/ohm	r
1	22	11 53	0 98
2	23	11 11	0 96
3	24	14 45	0 89
4	39	10 44	0 97
5	34	7 79	0 94
6	35	7 64	0 97
7	37	13 08	0 99
8	46	11 14	0 94
9	47	11 44	0 84
10	47	6 66	0 97
12	49	13 09	0 92
14	54	6 06	0 89
18	61	10 76	0 86
		$r_s = -0\ 407$	

those during monocular vision This type of experiment was performed with all the subjects in this study Measurable responses were obtained from all sub jects even the oldest ones In one case however (subject number 5) vigorous blinking during the binocular experiments produced artifacts that made the recordings unsuitable for analysis

Fig 5 shows some examples of the stimulus response relationship during binocular stimulation Diagram a and b are from the same subjects as Fig 3 a and *b* and 4 a and *b* A comparison between the responses during monocular and binocular vision showed that in most cases the convergence responses cor responding to a certain stimulus level were greater with binocular stimulation The same tendency but less obvious was observed in the ICG responses of some subjects The tendency of the responses to diminish with increasing stimuli at the higher levels was much less obvious during the binocular experiments especially concerning the convergence responses In fact only in one case could *one see a tendency for* the convergence response to become smaller with a stronger stimulus and this applied to the shortest *fixation distance only* In the other cases the relationship between stimulus and convergence response ap

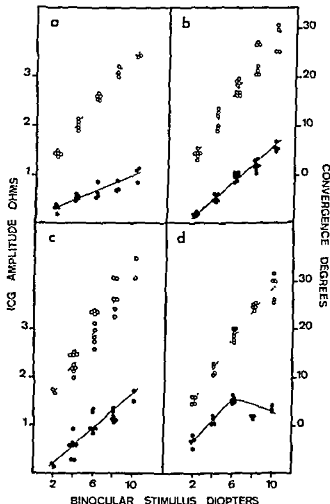


Fig 5

Stimulus response relationship during binocular vision in four subjects Diagrams a b c and d belong to subjects number 9 7 19 and 8 Symbols as in Fig 3

peared to be approximately linear or showed a slight upward convexity of the type seen in Fig 5 a b and d The individual differences in slope of the stimulus response relationship for convergence were much smaller with binocular fixation

Concerning the ICG amplitude relationship to stimulus there was in most cases a rising tendency throughout the stimulus interval studied Again the relationship seemed approximately linear in some cases and showed an upward convexity in some An example of an approximately linear relationship in one of the oldest subjects (age 62 years) is shown in Fig 5 c A tendency for levelling out at stimuli above 6 diopters was seen in cases number 1 3 4 13 14 and 18

Fig 5 d shows a striking difference between the stimulus response relation

ships for convergence and for ICG amplitude The convergence responses in crease with increasing stimuli but the ICG responses increase only up to the 6 diopters stimulus and at stronger stimuli a decreasing tendency is seen This was the only case in which such a strong discrepancy was found and the phe nomenon was reproduced on another occasion

Table III shows some statistical analyses of the stimulus response relation ship for the eye movement and ICG recording during binocular stimulation The mean responses show a decreasing tendency at higher stimulus intervals which is a result of the upward convexity of the stimulus response relationship observed in some cases This tendency is more obvious in the ICG responses than in the convergence responses

As a characteristic of the individual relationship between stimulus and res ponse at different ages a measure representing the area under the stimulus response curve was used (Fig 6) This measure of course does not describe all the variations in the curve form but there was no obvious age dependence of the type of curve and the area represents the average magnitude of the responses

Fig 7 illustrates the area representing convergence and ICG responses related to age There was no significant correlation between age and response (r_s = -0 252 and -0 166 for convergence and ICG respectively)

The results of the velocity measurements on the ICG changes during far to near and near to far changes of binocular fixation distance are exemplified at two stimulus levels in Fig 8 In Table IV all the values of the velocity mea surements are summarized The mean values are seen to be lower for near to far accommodation than for far to near accommodation at every stimulus level The velocities tend to be lower at low stimulus levels than at higher levels The rank correlation coefficient shows a tendency for a negative correlation be tween age and velocity in all columns and in near to far accommodation at the 6 and 8 diopter levels this tendency is statistically significant

Discussion

The stimulus response relationships during monocular stimulation exemplified in Fig 3 show some interesting features In some cases the increase of the sti mulus above moderate levels usually about 6 diopters did not result in a further increase of ICG amplitude but instead the responses diminished (Fig 3 a) This observation can be explained by an inability to focus on the target as it comes closer than the near point of accommodation which results in a weaker stimulus to accommodation Similar observations were described by *Alpern et*

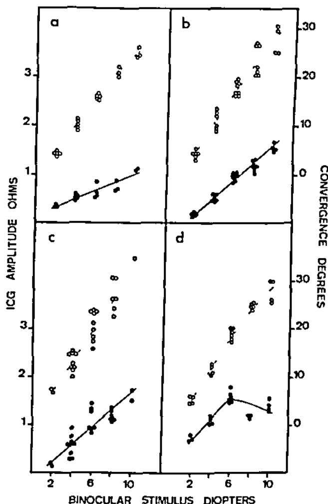


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Table III

Mean convergence and ICG responses to different binocular stimuli to near vision The total number of subjects was 17 since subjects 5 17 and 18 were eliminated because of difficulties in obtaining readings at all stimuli The right hand side of the table illustrates the distributions of the differences between the mean individual responses at the levels indicated at the head of each column

	Stimulus diopters					Stimulus interval diopters			
	2	4	6	8	10	4–2	6–4	8–6	10–8
Convergence response degrees N = 17 $\bar{X}$ s_x	5 0 26	12 1 0 44	18 6 0 66	23 9 0 93	28 1 1 16	6 6 0 24	6 5 0 26	5 3 0 42	4 2 0 64
ICG response ohms N = 17 $\bar{X}$ s_x	0 39 0 043	0 88 0 072	1 28 0 101	1 49 0 125	1 64 0 136	0 49 0 047	0 40 0 045	0 21 0 0[illegible]1	0 15 0 041

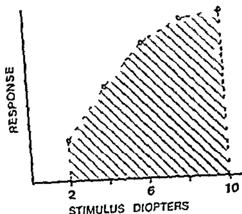


Fig 6

lethod for calculating the area under the stimulus response curve The circles rep e sent the arithmetic means of all responses at the stimulus levels indicated on the abscissa.

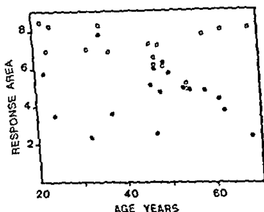


Fig ‹

Area under the binocular stimulus response curve related to age Arbitrary units were used to express the area which was calculated according to Fig f The open circles denote convergence responses the filled ones ICG resp nses

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	2	4	6	8	10	4–2	6–4	8–6	10–8
Convergence response degrees N = 17									
$\bar{X}$	5.5	12.1	18.6	23.9	28.1	6.6	6.5	5.3	4.2
$s_{\bar{x}}$	0.26	0.44	0.66	0.93	1.16	0.24	0.26	0.42	0.64
ICG response ohms N = 17									
$\bar{X}$	0.39	0.88	1.28	1.49	1.64	0.49	0.40	0.21	0.15
$s_{\bar{x}}$	0.043	0.072	0.101	0.125	0.136	0.047	0.045	0.051	0.041

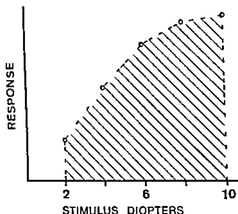


Fig 6

Method for calculating the area under the stimulus response curve The circles represent the arithmetic means of all responses at the stimulus levels indicated on the abscissa

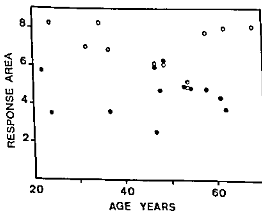


Fig 7

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$s_{\bar{x}}$	0 013	0 072	0 101	0 12	0 136	0 017	0 04	0 0 1	0 041

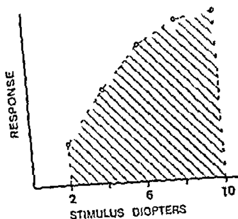


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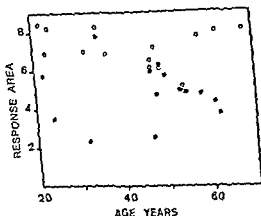


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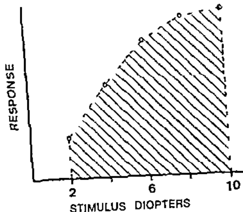


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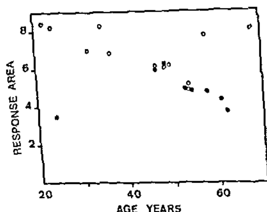


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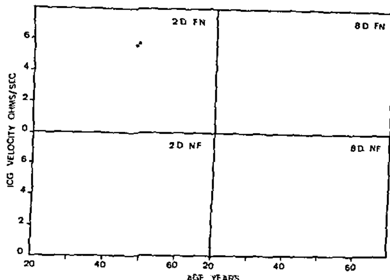


Fig 8

Maximum slope of the ICG curve during far to near (FN) and near to far (NF) changes of binocular fixation distance at the 2 and 8 diopter stimulus levels Each point represents the arithmetic mean of several changes

Table IV

Maximum slope of the ICG curve during changes of binocular fixation distance Th values were correlated to age by means of rank correlation The coefficients marked with an asterisk indicate a significant correlation

Far to near	Stimulus diopters				
	2	4	6	8	10
N	19	19	19	19	18
$\bar{X}$	2 81	3 49	3 74	3 61	3 49
$s_{\bar{x}}$	0 349	0 397	0 398	0 382	0 393
r_s	– 0 271	– 0 310	– 0 330	– 0 230	– 0 253
Near to far					
N	11	13	12	11	9
$\bar{X}$	1 17	1 96	2 66	2 85	3 04
$s_{\bar{x}}$	0 115	0 258	0 354	0 364	0 469
r_s	– 0 473	– 0 312	– 0 652*	– 0 618*	– 0 500

focus on the target accurately This is a probably explanation of the increase in the responses beyond the accommodation amplitude in Fig 3 b

In this material it was not possible to see any obvious age relationship to the EOG or ICG amplitude during monocular stimulation but the cases in which no measurable responses could be recorded were found among the older subjects so it seems safe to conclude that the ciliary muscle responses during monocular stimulation were less in individuals above the age of 55 than below this age in the material investigated here This is hardly surprising considering the inability to focus at close distances which is the result of presbyopia

The relationship between monocular accommodation in diopters and accommodative convergence (response AC/A ratio) has been investigated by several authors including *Alpern et al* (1959) and *Ripps et al* (1962) and shown to be approximately linear over an intermediate range of stimuli The present investigation has shown that in most cases the individual relationship between ICG amplitude in ohms and accommodative convergence in degrees can be described by a straight line In no case could an obviously non linear relationship be observed This means then that within the accommodation amplitude of the subject an increase of physical accommodation is accompanied by an increased ICG amplitude It was shown previously (*Swegmark & Olsson* 1968) that the ICG reflects the ciliary muscle activity and the present study indicates that in most cases the ICG represents approximately quantitatively what has been called the physiological accommodation

Alpern et al (1959) demonstrated a departure from linearity of the response AC/A ratio at higher levels of accommodation stimulus in prepresbyopic subjects When the stimulus increased above a certain level the convergence response increased more than the accommodation response This phenomenon is ascribed to the physiological lens sclerosis that restricts the physical accommodation response while the convergence response is free to increase with a further increase of stimulus The authors propose that the motor innervations to accommodation and accommodative convergence are linearly related to each other

It is interesting to note that in the present investigation no departure from linearity could be observed in the accommodative convergence – ICG amplitude relationship at the higher response levels In several cases the largest responses corresponded to a fixation distance shorter than the near point of accommodation of the subject If the ciliary muscle force had decreased parallel to the lenticular sclerosis one would have expected the ICG responses to increase less than the convergence resulting in a systematic departure from linearity at the higher levels The data of the monocular experiments thus do not indicate that the maximum contraction ability of the ciliary muscle decreases when a person gets older within the age interval studied (up to 61 years)

The data of Table II give some information about the relation between the innervation to the ciliary muscle and the resulting contraction of the muscle Assuming a linear relationship between ciliary muscle innervation and the in

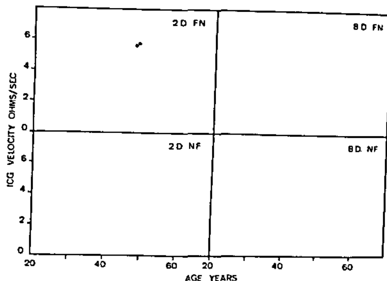


Fig 8

Maximum slope of the ICG curve during far to near (FN) and near to far (NF) changes of binocular fixation distance at the 2 and 8 diopter stimulus levels. Each point represents the arithmetic mean of several changes

Table IV

Maximum slope of the ICG curve during changes of binocular fixation distance. The values were correlated to age by means of rank correlation. The coefficients marked with an asterisk indicate a significant correlation

Far to near	Stimulus diopters				
	2	4	6	8	10
N	19	19	19	19	18
$\bar{X}$	2.81	3.49	3.74	3.61	3.49
$s_{\bar{x}}$	0.349	0.397	0.398	0.382	0.393
r_s	−0.271	−0.310	−0.330	−0.230	−0.253
Near to far					
N	11	13	12	11	9
$\bar{X}$	1.17	1.96	2.66	2.85	3.04
$s_{\bar{x}}$	0.115	0.258	0.384	0.364	0.469
r_s	−0.473	−0.312	−0.652*	−0.618*	−0.500

focus on the target accurately. This is a probably explanation of the increase in the responses beyond the accommodation amplitude in Fig 3 b

vergence responses were obtained in all subjects during binocular stimulation also in the older persons in whom no measurable responses could be recorded during monocular stimulation In the other cases the difference in responses was usually greatest for convergence

Fig 7 and Table III disclose a rather large variability of the responses during binocular vision To investigate this fact a separate analysis of the results from two different days was made in the cases in whom complete data were obtained on both occasions Concerning the ICC responses the variance of the individual means from two different days in 13 subjects was compared to the total variance This was made at each stimulus level by means of a one variable components of variance model The fraction of the total variance of the ICG responses depending on the variance within individuals amounted to an average of 18 % (arithmetic mean of the percentages found at each stimulus level) This means that errors of measurement and day to day variations were small compared to the inter individual variations The corresponding value for the convergence measurements was 41 % in 9 subjects

The decrease in the responses at higher stimulus intervals demonstrated in Table III deserves some comment.

A curvilinear relationship between the stimulus expressed in diopters and the response in degrees is to be expected for geometric reasons A simple calculation shows that if the interpupillary distance is assumed to be 65 mm and the center of rotation of the eyeball is supposed to be located 13.5 mm behind the corneal surface a change of fixation distance from 50 to 25 cm demands an increase of convergence of 6 4 degrees A change from 12 5 to 10 cm corresponds to a convergence change of only 4 7 degrees in spite of the fact that the increase in stimulus is 2 diopters in both these examples This means that the relationship between stimulus and vergence ought to show a convexity upwards when expressed in the units used in this study The change of distance from 200 to 50 cm corresponds to a vergence change of 5 3 degrees which explains the rather low value in the 2 diopter column

Concerning the mean ICG responses accounted for in Table III the difference in increase of the responses at low and high stimulus intervals is even more pronounced This may be due partly to the assymmetry of the experimental setup as is shown in Fig 1 The stimulus values used in this study are based upon the distance between the test eye (A) and the near target (C) The distance between the target and the opposite eye (B) is larger and this difference gets more pronounced as the target approaches the eyes In binocular testing and particularly at short distances it is possible that the subject chooses to focus on the target with the opposite eye since this requires less demand on the accommodation In that case the effective stimulus will be less than the one corresponding to the target distance to the test eye Assuming an interpupillary distance of 65 mm and a center of rotation 13 5 mm behind the cornea a 2

nervation to accommodative convergence and that this relationship does not change throughout an individual's life the convergence response gives information about the ciliary muscle innervation If as age progresses ciliary muscle changes result in a decrease in response of the muscle to a unit innervation th relationship between accommodative convergence and ciliary muscle activity ought to change In older subjects a unit ciliary muscle contraction ought to be associated with a larger accommodative convergence As the ICG amplitude is a measure of ciliary muscle activity the relationship between accommodative convergence and ICG amplitude ought to be age-dependent The b values in the table are measures of this relation and they ought to be higher in the older subjects as a result of ciliary muscle weakness As can be seen from the rank *correlation coefficient there is no such tendency*

Thus the present investigation does not indicate that the relation between *the innervation to the ciliary* muscle and the resulting activity *of the* muscle changes with age

The relation between monocular stimulus to accommodation and accommodative convergence (stimulus AC/A ratio) can be considered as a measure of the innervation relationship between accommodation and accommodative convergence *Alpern* (1962) has summarized some studies on the possible age dependence of the stimulus AC/A at ages up to 50 years He concluded that if there is any change at all in the ratio this change must be quite small and in the direction of a decrease in the AC/A as age progresses This conclusion is valid also for the "b" values found in the present study which includes also a few subjects above 50 years of age but the small material investigated does not permit more detailed analysis However the relationship between accommodative convergence and ICG amplitude offers a new approach to analysis of the accommodation convergence synkinesis with possible clinical applications

Also the binocular experiments in this study are interesting in connection with the question of the possible age dependence of ciliary muscle function If more ciliary muscle contraction were necessary to bring about a unit change of refraction in the older subjects than in the younger one would expect a greater ICG amplitude for the same change in fixation distance with increasing age Fig 7 does not show any obvious tendency for the ICG amplitudes to be larger in the older subjects The statistical analysis verified this impression as no significant correlation was found between age and the response area" (Fig 6) This was also true for the convergence responses

The binocular experiments of this study thus do not support the view that as age progresses more ciliary muscle activity is needed to bring about a unit change of refraction

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Judging from the results of the present study the morphological changes mentioned above do not affect the contractile ability of the ciliary muscle appreciably before the age of 60 The material does not permit any conclusions about the ages above this level although the oldest subject showed generally low ICG amplitudes (Fig 7)

The measurements of the slope of the ICG curve during changes in fixation distance give information about the velocity of the ciliary muscle contraction and relaxation

The results presented in Table IV indicate that the near to-far change (relaxation of ciliary muscle) is slower in older subjects at least at higher levels of stimulation A similar tendency can be seen in the far to near data, but it is not obvious enough to permit any generalized conclusions *Schubert* (1955) by his ciliary potential recording technique found that a presbyopic subject showed a slower change of potential during near to far accommodation than did some younger subjects He also found a slower rate of change during near to-far accommodation than during far to near accommodation which is also the impression gained from the present study (Table IV)

The velocity differences are the only age dependent changes in ciliary muscle function that have been established by this investigation and they are probably the result of the histological changes mentioned above

Summary and Conclusions

The method of impedance cyclography (ICG) *was used for investigating* ciliary muscle function during changes of monocular and binocular fixation distance in a material of approximately emmetropic subjects *with an* age ranging between 17 and 65 years Synchronous recordings of eye movements were made by means of electro oculography

The contractile ability of the ciliary muscle was shown to remain essentially unimpaired up to the age of 60

Assuming a constant and inflexible relation between the innervation to the ciliary muscle and to accommodative convergence the present *investigation* does not demonstrate any change in the relation between the ciliary muscle innervation and the actual activity of the muscle with age

The speed *of relaxation* of the muscle *during* near to far changes *of* binocular fixation distance was lower in the older subjects than in younger ones with in the age interval studied

diopter stimulus to the test eye corresponds to a stimulus of 1 9S diopters to th opposite eye At the 6 diopter level the difference will be 0 39 diopters and at the 10 diopter level 1 47 diopters This may account for some part of the de crease of responses at the higher stimulus intervals At levels above 6 diopters, however there still remains some nonlinearity of the curve corresponding to the mean stimulus – ICG response relationship This is the result of the up ward convex relationship found in some of the subjects An extreme example of this is shown in Fig 5 d This may be the result of a lag of accommodation behind convergence at close fixation distances Owing to difficulties in focus ing the stimulus to accommodation may diminish and the stimulus to conver gence will dominate

From this study it is obvious that the ciliary muscle contraction continues to be a part of the near vision reflex at an age when the lens has virtually lost its ability to change its optical properties This confirms the view that changes in the lens are the cause of presbyopia and that ciliary muscle changes do not normally have any influence on this process

The possibility still remains that the ciliary muscle force declines continuously during life without affecting the physical amplitude of accommodation This should result in a decrease of physiological accommodation and if this decline occurred faster than the lens changes the result would be a continuous decrease of the latent ciliary force as proposed by *Goldmann* & *Aschmann* (1946) *Alpern* (1962) considered it likely that a certain atrophy from lack of use would take place in the ciliary muscle as age progresses and that at all ages almost maximum shortening of the muscle would be required to produce maximum ac commodation This view is not supported by the present investigation For example Fig 5 c shows an increase of ciliary muscle activity at very close fixa tion distances far closer than the near point of accommodation for this 62 year old man The fact that the greater part of this muscular activity is without ef fect on the optical properties of the lens obviously has not resulted in any con siderable decrease of function from lack of use This is in accordance with the widely accepted hypothesis that there is a close relationship between the inner vation to convergence and to the ciliary muscle Even in old people the near vision reflex is accompanied by innervation both to convergence and to ciliary activity From this point of view an atrophy from lack of use could only result from a decrease in convergence requirement However as a part of generalized senile changes one can of course expect a certain amount of atrophy of the ciliary muscle as well as of most other tissues of the body

Stieve (1949) in an extensive histological investigation found differences in the appearance of the ciliary muscle at different ages and above 55 years se nile atrophic changes could be demonstrated *Marchand* (1964) found increasing hyaline changes in the muscle after the age of 40 and *Rother* & *Leutert* (1965)

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From The Bacteriologic Laboratory (Head V Frølund Thomsen)
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DISINFECTION OF GOLDMANN S APPLANATION TONOMETER PRISM BY MEANS OF ULTRAVIOLET LIGHT

BY

V FRØLUND THOMSEN and M S NORN

It has been shown that Goldmann s applanation tonometer prism becomes contaminated in use and that the usual procedure of wiping the prism with a swab of cotton moistened with merphene (a solution of phenylmercuric borate (1 32 000) does not hinder transmission of this contamination from patient to patient (*Norn & Thomsen* 1968)

It is not possible to perform an effective and certain sterilization of the prism by heat as can be done with the Schiøtz tonometer using the sterilization apparatus described by *Mahneke & Pieuerts Eriksen* (1961) since the Goldmann tonometer is made of thermoplastic material with cemented end surfaces which are damaged by heating

Sterilization in the intervals of use ought not to require more than a few minutes This excludes the possibility of sterilization by means of ethylene oxide and formalin as such procedures take from one day to the next involving an excessive demand for prisms and for economic reasons this cannot be satisfied The same is the case with the usual radiation sterilization in a reactor by means of gamma irradiation On the other hand a cobolt source could yield sufficient energy but is inconvenient in practice

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Read in an abbreviated form at the common meeting between the Danish Ophthalmological Society (4 th meeting) and the South Swedish Ophthalmological Club in Lund ⁹ n l of February 1969
Received April 11th 1969

Presbyopia depends upon lens changes and ciliary muscle changes do not normally influence the *physical accommodation amplitude*

This study indicates that the amount of ciliary muscle activity needed for a unit change of refraction does not increase with age

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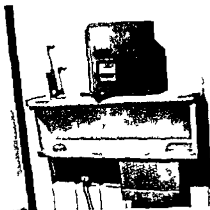


Fig 1
Apparatus for ultraviolet irradiation of applanation tonometer prisms
Goldmann's applanation tonometer prism is to the left of the apparatus before being inserted The resistance is on the shelf

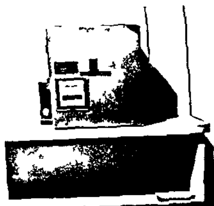


Fig 2
Apparatus for ultraviolet irradiation of applanation tonometer prisms
The applanation tonometer is in place to the left of the apparatus

should be replaced The lamp can burn for 6000 hours corresponding to about one year's clinical use The apparatus is connected to a variable resistance (20 × 15 × 8 cm) and is placed on a shelf close to the slit lamp used for the applanation tonometry

The *disinfecting power* of the apparatus was determined with respect to 6 se

Ultraviolet light is germicidal the activity lying in the range of wave lengths 2000 Å to 3100 Å the "abiotic" region where both protozoa fungi bacteria and viruses are killed (*Spector* 1956 *Oberdoerster* & *Thielecke* 1965) The optimum region lies around 2650 Å In the commercial UV lamps 85 % of the germicidal radiation is produced at a wave length of 2537 Å

Lawrence & *Bloch* (1968) recommend UV light for the inactivation of micro organisms which are localized on surfaces or suspended in fluids into which the UV rays can reach

Hill et al 1969 inactivated poliovirus T_1 in seawater by means of ultraviolet light and found 99 98 % reduction in 15 7 sec

The end face of the prism is quite flat and can be cleaned by a simple procedure before carrying out the disinfection According to *Lawrence* & *Bloch* this can be done by UV light which possesses the advantage that the material is exposed to a mild treatment As the initial bacterial count on the end surface of the prism can be reduced to a small value an inactivation factor of less than 10^6 should be acceptable so that the UV light can maintain sterility until the apparatus is to be used once again

Inactivation by UV light of microorganisms which have dried into plastic surfaces has not been studied previously It was therefore decided to examine the sterilizing capacity of an apparatus specially constructed by us following on a known massive contamination of the end surface of a tonometer prism by means of known bacterial strains

Material and Method

The apparatus was constructed and modified (repeatedly) by Engineer *Bent Hansen*

The apparatus consists of an UV light unit (*Hanau*) placed in a metal box 20 cm long 21 cm high and 15 cm wide An aperture in the end face 2 cm high and 1 3 cm wide corresponds to the applanation prism and opposite this surface there is a metal rail intended for the introduction of the tonometer The distance between the end surface and the inserted tonometer and the source of light is 10 cm (other distances have also been examined in the tests described below) A concave mirror placed behind the light source focusses the light rays on the front surface of the prism A *time recorder* is built into the box to indicate the total number of hours the lamp has burned to determine when it

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* Engineer Bent Hansen (Messrs Sorensen & Hald) is thanked for his tireless and invaluable assistance with the construction of the apparatus

Globigii kindly made available by Dr *Ebbe A Christensen* Statens Seruminstitut Copenhagen Quantitative determinations were made by viable counts of the individual impressions

A piece of filter paper is moistened with a serum broth suspension of *S faecium* or a saline suspension *B subtilis* The prism is contaminated by pressing on this paper and an impression is then made on the sterile agar surface Using a cork bore a cylinder is cut out around the impression and by means of forceps this cylinder is placed in 2 0 ml filtered broth in a test tube The tube is shaken for 2 minutes to release the bacteria from the agar surface The viable count is determined by series dilution from each of the dilutions 1 10 1 100 and 1 1000 0 1 ml is subcultured on 5 % blood agar It is spread on the surface by a sterile rod and the blood agar incubated at 35 C for 48 hours The colonies are then counted and the viable count per impression is calculated The determination is made daily so that each day there are 2 control tests and 3 irradiation tests corresponding to each exposure time

The apparatus has also been examined with a clinical material

Results

Table 1 shows the results of the experiments with the vegetative clinical strains from which it appears that in all cases there was complete bacterial

Table 1

Applanation tonometer prisms exposed to ultraviolet light after contamination with a suspension of bacteria

	Control	Exposure time in minutes				
		1/2	1	2	3	4
S aureus	4/4	11/16	0/16	1/16	0/16	0/16
E coli	4/4	0/16	0/16	0/16	0 16	0/16
Klebsiella	4 4	11/16	0/16	0/16	0/16	0/16
P aeruginosa	4/4	0/16	0/16	0 16	0/16	0/16
B anitratum	4/4	0/16	0/16	0 16	0/16	0/16
C pseudodiphtheriticum	3 3	0 9	0/ 9	0 9	–	–

The figures in the numerator give the number of prisms with growth after incubation at 35 C for 48 hours
Denominator number of prisms examined

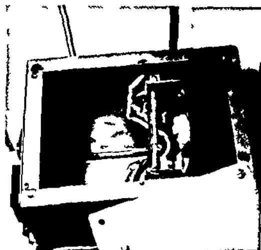


Fig 3

Apparatus for ultraviolet irradiation of applanation tonometer prisms
The top plate of the apparatus has been removed so that the inside can be seen To the right UV burner with concave mirror To the left the end surface of the applanation prism can just be seen

lected vegetative clinical strains" *S aureus E coli Klebsiella P aeruginosa B anitratum* and *C pseudodiphthericum*

A piece of filter paper is placed on the bottom of an empty, sterile Petri dish and then soaked with broth in which a bacterial culture has been suspended to give a density of 10^9 coli bacilli per ml

The applanation tonometer prism is pressed against the filter paper and then placed in the apparatus After the exposure time the end surface of the prism is pressed against the surface of a solid substrate (5 % blood agar) As a control an impression is made without prior exposure to UV light

The plates are incubated aerobically at 35° C for 48 hours and then inspected for colony growth in the area corresponding to the impressions produced by the prisms

Four impressions were made for each exposure time giving a total of 16 possibilities for growth as 4 prisms are examined on each agar plate

However it is not sufficient that the apparatus should effectively kill the usual clinical bacterial strains It is necessary that viruses in particular the adenovirus which causes the feared epidemic keratoconjunctivitis should also be killed

The culture of virus is a difficult process so that preference has been given to testing certain bacteria which are particularly resistant to irradiation

The *sterilizing power* of the apparatus was determined with respect to a radiation resistant *Streptococcus faecium* and dried spores of *Bacillus subtilis*

Table 3

Applanation tonometer prisms contaminated with a suspension of *Str faecium* and irradiated with ultraviolet light

Day	Control	Exposure times in minutes					
		1/2	1	2	4	8	30
1	4.38	3.85	<1	1.23	<1	<1	1.00
2	5.89	0.97	2.88	2.86	4.29	3.27	<1
3	5.93	2.97	3.66	2.08	2.75	2.11	1.33
4	6.08	3.68	3.13	2.97	2.11	1.12	1.49
5	5.13	4.09	3.19	3.47	<1	1.45	0.40
6	4.[illegible]9	0.43	<1	<1	<1	<1	<1
7	3.37	0.43	<1	<1	<1	<1	<1
8	5.21	2.18	1.49	2.05	2.87	2.25	0.85
9	5.49	3.76	3.08	2.62	1.93	2.64	<1
10	4.99	–	–	–	–	–	1.07
11	4.17	–	–	–	–	–	0.65

The figures indicate $\log_{10}$ of the colony count after incubation at 37° C for 48 hours

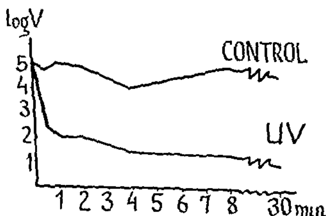


Fig 4

Inactivation curve for S faecium with ultraviolet light Abscissa time for ultraviolet irradiation in minutes Ordinate log 10 *of the viable count*

tion tonometry the prism is wiped with a piece of dry cotton and irradiated with UV light for at least 2 *minutes* often considerably *longer* determined by

death after irradiation for 3 minutes After irradiation for 2 minutes 1 of the 16 impressions with *S aureus* continued to be infected After irradiation for half a minute the prisms with *E coli* *P aeruginosa* *B anitratum* and *C pseudodiphtheriticum* showed no growth

The effect on a spore suspension is shown in table 2 where the surviving organisms are expressed as the logarithms to base 10 of the viable count A fall in the viable count is seen from about 10^4 10^5 to 10^1 10 viable organisms per prism after 2 minutes

Table 3 shows the results of the experiments with the radiation resistant *S faecium* These experiments were carried out for 11 days with a exposure time of up to 30 minutes A considerable fall is seen in the viable count during the first minutes but when the irradiation time is increased up to 30 minutes there is only an insignificant further reduction

Fig 4 is a graphic illustration of the reduction in viable count as a function of the exposure time where the upper curve indicates the bacterial count on the prism when this is placed in the apparatus with the lamp switched off The lower curve shows the inactivation curve after irradiation Both curves are recorded as the mean of the determinations on all experimental days During the first minute there is a steep fall in the viable count particularly pronounced during the first few seconds Inactivation then ceases and the curve continues almost horizontally While the reduction factor ($\log_{10}$) is about 3 during the first minute this increases to only about 4 in 30 minutes i e a difference of only 1 The figure shows that a reduction factor of 10^6 would require an exposure time of several days

The *clinical material* comprises prisms from 255 patients After the applana

Table 2

Applanation tonometer prisms contaminated with a spore suspension of *B subtilis Globigii* and irradiated with ultraviolet light

	Exposure time in seconds				
	5	15	30	60	120
Control	4 17	3 96	3 45	4 85	5 15
1	4 11	3 64	4 15	2 62	2 64
2	4 13	2 78	3 06	2 64	1 60
3	4 76	2 26	2 34	2 82	1 60

The figures indicate $\log_{10}$ of the colony count after incubation at 3 °C for 48 hours

Table 5

Cultivation from applanation tonometer prisms treated with ultraviolet light after use and before being used again.

	2 UV light 10 cm	2 UV light 1.3 cm	2 UV light 4.5 cm	1 UV light 10 cm	Alcohol pretreatment 10 cm	Total without alcohol
Growth	*1*	8	2	*3*	2	*14*
Sterile	10	107	42	82	110	241
Total	11	115	44	85	112	255
Percentage non sterile	9 %	7 %	5 %	4 %	2 %	5.5 %

Discussion

The purpose of disinfection of the applanation tonometer prism is to hinder transfer of infection from patient to patient by means of the surface of the prism and to keep the prism free from pathogenic bacteria until it is applied to the eye.

UV irradiation reduces the viable count on the prism by more than 99 %, which is insufficient for disinfection. The occurrence of more than 10 000 viable organisms on the surface of the prism is probably not rare even without recognisable infection. To ensure against the transmission of virus infection a total inactivation factor of more than 1 000 000 is required in order to achieve satisfactory disinfection for daily use.

UV light alone is insufficient since the inactivation curve of the radiation resistant *S. faecium* which is used has its greatest slope initially. The slope decreases strongly in the course of the first few minutes and after 2 minutes the curve is almost horizontal. This very slight slope would require an exposure for more than 100 hours if an inactivation factor of 1 000 000 had to be reached. The form of this inactivation curve differs essentially from the inactivation curve for *S. radiodurans* exposed to gamma radiation where *Christensen* (1964) found that the initial slope was the smallest value. In the latter case it would be rational to prolong the irradiation period. With the course of the inactivation curve shown in fig. 4 only little would be achieved by prolonging

the time of the next tonometry The prism is removed from the light box and its end surface carefully pressed 4 times against the 5 % blood agar plate whereby it leaves clear traces on the surface of the substrate The plate is then incubated at 35° C for 2 days

Of the 255 prisms examined 241 were sterile and in 14 cases (5 5 %) bacterial growth was demonstrated

It may be stated for comparison that on cleaning with merphene after the applanation tonometry 70 % of the prisms were found to be contaminated out of 280 examined (*Norn & Thomsen* 1968)

After 20 minutes in merphene 35 % of 60 prisms was contaminated (unpublished investigations)

As table 4 shows the organisms involved were mainly gram positive cocci in clusters which did not coagulate horse citrate plasma or ferment mannitol

Use of two radiation sources placed 10 cm from the end surface did not reduce the contamination frequency as 9 % of the prisms produced growth against only 4 % with a single source (table 5)

The distance to the source of radiation did not affect the contamination frequency as 5 % were found to be contaminated at a distance of 4 5 cm and 7 % with a distance of only 1 3 cm between the two UV tubes and the end surface of the prism

Table 4

Bacterial findings from applanation tonometer prisms exposed to ultraviolet light after use and before being used again (a total of 255 determinations)

UV light	Distance	Bacteria	Colonies
2	10 cm	Gram pos cocci in clusters mannite citrate plasma	2
2	1 3 cm	Gram pos cocci in clusters mannite citrate plasma	5
2	1 3 cm	Gram pos cocci in clusters mannite citrate plasma	1
2	1 3 cm	Gram pos cocci in clusters mannite citrate plasma	6
2	1 3 cm	Gram pos cocci in clusters mannite citrate plasma	2
2	1 3 cm	Gram pos cocci in clusters mannite citrate plasma	5
2	1 3 cm	Gram pos cocci in clusters mannite citrate plasma	1
2	1 3 cm	Gram pos diplococci clusters mannite citrate plasma	7
2	1 3 cm	Gram pos diplococci clusters mannite citrate plasma	2
1	4 5 cm	Gram pos coryneform rods	1
1	4 5 cm	Gram pos cocci in clusters mannite citrate plasma	1
1	10 cm	Gram pos cocci in clusters mannite citrate plasma	1
1	10 cm	Gram pos diplococci in clusters	3
1	10 cm	Gram pos cocci in clusters mannite citrate plasma	1

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the period of irradiation The same holds when the effect is increased with two or more irradiation lamps or with the lamps closer to the prism *Oberdoerster & Thielecke* (1965) used *B pseudoanthracis* and *Aspergillus oryzae* and found linear inactivation curves with doses up to about 25 000 μW sec/cm but a decreasing effect with increasing irradiation doses Their differences were only small when compared with those found in the present study

It is difficult to explain the slope of the inactivation curve The appearance of the curve might suggest that the culture was composed of two different cultures namely a very sensitive population comprising more than 99 % of all organisms and a resistant culture comprising less than 1 % of the entire bacterial mass It would be possible for such a distribution to arise if the end surface of the prism had microscopic scratches corresponding to 1 % of its area as the bacteria in these scratches would then be protected against the irradiation

A chemical disinfectant such as formalin chloramine or alcohol will ensure effective disinfection provided the procedure includes cleaning The difficulty of chemical disinfection is that the disinfectant – on account of the eyes – has to be removed before the prism is used again whereby the risk of contamination arises

A combination of *chemical disinfection* and irradiation sterilization might therefore appear convenient The chemical disinfection provides an adequate cleaning and the viable count on the prism end surface is reduced to low values The prism is then placed in the irradiation box for air drying whereby it is further disinfected and remains sterile till the next time it is used

As a chemical disinfectant absolute alcohol is recommended since it is strongly germicidal and has a broad spectrum as well as being volatile so that it is easily removed by simple air drying Complete alcohol evaporation and adequate UV effect is achieved after an irradiation lasting for at least 4 minutes

The following procedure is followed after using the prism it is dried carefully with a swab moistened in alcohol so that any visible contamination is removed The end surface of the prism is dipped into absolute alcohol the excess alcohol shaken off and the prism placed in the UV box where it remains at least 4 minutes before next use The alcohol evaporates at room temperature in the course of 2 minutes (10 experiments) but will otherwise hardly reduce the effect of the UV light as absorption in alcohol is minimal Drying is omitted as this would involve risk of further contamination

After UV irradiation alone 5.5 % of all prisms continue to be contaminated The pretreatment with alcohol reduces the frequency to about 2 % (table 5) which suggests that the 3.5 % are real contaminations and not laboratory contaminations which otherwise must occur with the procedure employed

The bacteria found correspond also very well to those previously demonstrated on the prism (*Norn & Thomsen* 1968) Of the 2 % of contaminations

which are found after the disinfection some must arise from the investigation itself

After daily use of the same applanation prisms for 9 months damage to the end surface (crackling) was found in two prisms Both of them were used in experiments with a short distance between the light source and the prism (1 3 cm) In using UV radiation (*Follmann* 1969) one must reckon with an increased consumption of prisms presumably 2 4 per annum The prize per prism is approximately 1?0 Danish Crowns *Alcohol does not appear to damage the prism in the procedure used here*

Tonometer irradiation in the ultraviolet light box can be used as a routine procedure Disinfection of the end surface of the prism with absolute alcohol prior to the UV irradiation can be kept for those cases where there is a clinical suspicion of infection

Alcohol disinfection without UV light should not be carried out as the prism must only be used when the alcohol has evaporated completely and may then have become non sterile

Summary

Apparatus is described for disinfection of Goldmann s applanation tonometer prism by means of ultraviolet light

In clinical experiments 5 5% of the prisms were contaminated after disinfection of the apparatus while 70% were contaminated after conventional cleaning

Suspensions of clinical bacteria were killed completely within 3 minutes (*S aureus E coli Klebsiella P aeruginosa B anitratum C pseudodiphtheriticum*)

The viable count of a radiation resistant *S faecium* was reduced by a factor of 1000 in the course of 1 minute while the viable count of a *B subtilis* spore suspension was reduced by a factor of 1000 in about 2 minutes

Ultraviolet irradiation provides a clear destruction of bacteria on the end surface of the applanation prisms but is hardly sufficient in the case of massive contamination by virus

An adequate degree of safety can be achieved by treating the end surface of the prism with absolute alcohol and then irradiating the prism with UV light for at least 4 minutes prior to carrying out the next applanation

The apparatus described for the ultraviolet irradiation of Goldmann s applanation ton meter prism is produced by Messrs *Sorensen & Hald* Frederiksberggade 28 1459 Copenhagen K (construction No 15??) Prise approximately 7000 danish crowns

Christensen E A Radiation resistance of enterococci dried in air Act path et micro biol scandinav *61* 483 86 (1964)

Follmann P (Budapest) personal communication (1969)

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Norn M S & V Frolund Thomsen Contamination of eye drops used for vital staining (Bacteriological analyses of Rose Bengal Fluorescein Alcian Blue and Fluorescein Novesin instilled from a Needle Mounted tube) Acta Ophthal *45* 650 657 (1967)

Norn M S & V Frolund Thomsen Contamination of applanation tonometer prism Acta Ophthal *46* 712 720 (1968)

Oberdoerster F & K-H Thielecke Über praktisch anvendbare Methoden zur und Bewertung von UVC Bestrahlungsanlagen Z ges Hyg *11* 723 732 (1965) und *ibid* 817 828 (1965)

Spector W S (Editor) Handbook of Biological Data Philadelphia 1956 pag 474

Pouliquen Yves Atlas d'Histologie et d'Ultrastructure du *Globe Oculaire* Masson et Cie Paris 1969 (174 pages 158 *figures price 60 Fr*)

In eight instructive well illustrated chapters the book provides a short schematic sur*vey of the structure and ultrastructure* of normal ocular tissues

The book does not pretend to give a critical *discussion nor complete lists of refe*rences It is meant as a preliminary introduction to the topic and because of the many excellent micrographs and electronmicrographs it is a highly stimulating one

Niels Bulow

Rolger and Sinclair *Metabolic and nutritional eye diseases* 419 p illustr *Price* $ 14 50 Charl Thomas Springfield U S A

This book is written for opthalmologists to outline the biochemical abnormalities that are basis of the eye diseases The disorders are classified so that the clinician can most easily find the informations he seeks The chapters comprise Nutrition and metabolism disorders of protein metabolism carbohydrates and fat metabolism vitamin deficiensies mineral metabolism autoimmune diseases and finally undernutrition

It is astonishing how much biochemistry is involved *in so many eye diseases*

Holger Ehlers

Sachsenweger P Sehubungen Ein Bilderbuch 2nd ed 95 pages with 110 illustrations Johan Ambrosius Barth Leipzig 1969 Price 9 60 DM

The illustrations are intended to serve as visual exercises for weaksighted patients and squinters Daily exercises develop the child s sense of detail and the series of illustrations seem entertaining and absorbing A number of the pictures are pleasing *from the* purely artistic point of view

The exercises are for children in the age range 4–10 years *Holger Ehlers*

Saraux H and Biais Precis d'ophtalmologie 978 pages 578 figures 3 plates Masson et Cie Paris 1969 (150 Fr)

The book is in 6 parts I Diagnostic methods II Diseases of the eye and ocular adnexa III Neuro ophthalmology IV The eye and general pathology V Traumatology VI Treatment

Apparently this book is meant to be a concise presentation of *the discipline for the* postgraduate *education of* specialists and seems to be suited for this purpose It does not discuss many theoretical considerations or possibilities but gives a brief and clear account of the instruments and their application, the manifestation of diseases and the possibilities of treating them

An ample list of references is included to guide those who want to make *further* studies but not many authors *are quoted* in the text *Holger Ehlers*

Taubenhaus Leon J and Anne A Jackson Vision Screening of Preschool Children Charles C Thomas Springfield Illinois U S A 1969 106 pages price $ 5

This publication is based upon experience from the Brookline, Massachusetts, Preschool Vision Screening Research Study This study comprised almost 5000 children, and 160 volunteer sight screeners" collaborated It is meant to be a guidance for community leaders who wish to start a similar programme in their own community

The authors point out that many children start school with a visual defect. In about 4 % of all children this defect is an amblyopia ex anopsia a condition which may be corrected if treatment is instituted before the age of 6 years

Owing to the large number of children the detection of impaired vision cannot be left exclusively to the doctors The solution is communally organized vision screening of preschool children performed by volunteers If this screening reveals impaired vision, the children are referred for further examination and treatment, to an ophthalmologist.

The book comprises orientation concerning the object and organization of the vision screening guidance for the training of the volunteers and a description of 4 different vision tests for preschool children

This book is based upon the conditions in the U S A and is intended primarily for American readers However it is of universal interest in emphasizing the importance of detecting and treating visual defects before school age *Eva Rindziunski*

Bonamour G M Bonnet P Bregeat and P Juge La papille optique 531 pages figures 16 plates in colour Masson et Cie Paris 1968 Price 150 fr

It is remarkable that the references appended to each part do not go further back than 10 years The first part deals with anatomy physiology and malformations Thereafter oedema atrophy drusen and traumas are described The illustrations have been chosen with care and are well reproduced The coloured plates contain many reproductions of typical eyeground changes The importance of being aware of the existence of refraction conditioned scotomas is rightly emphasized in order to avoid unnecessary exploratory neurosurgery It is a pleasure to read the fifty odd pages on the aetiology of papilloedema A description of pre and peri papillary newformation of vessels in long term diabetes might have been included

This well written and beautifully illustrated textbook bears witness to its authors extensive experience within ophthalmology as well as neuroophthalmology

Viggo A Jensen

Castroviejo R Keratoplastik Georg Thieme Verlag Stuttgart 1968 453 pages 1 3 illustrations some in colour Size 28 × 22 cm Price DM 168 – Translated by F Hollwich

Few ophthalmic surgeons if any have performed as many operations on the cornea as Castroviejo His experience from 3000 keratectomies and 5000 keratoplasties form the basis of this book which was first published in Spanish in 1964

A vast number of illustrations gives the book the caracter of an atlas The lucid and instructive drawings together with a brief and concise text admirably describes the various forms of keratectomy keratoplasty and keratoprosthesis operations used by the

author *Special at ention* is paid to the technical part of the operations and to the choice of *instruments* *Ample space* is devoted to operative and postoperative compli cations and their mana ement. One miss however a description of the operating microscope and the resulting refined operative and suturing technique which has become of such importance *especially in corneal surgery* *Nevertheless it is a book which may be earnestly recommanded to every ophthalmologist who desires to enter into the* technical details of corneal surgery

A collection of excellent colour plates illustrating eyes before and after the various operations appear as an appendix The publishers have provided the book with a first class styl ng and prin ing

Torstein Bertelsen

Klein E Die Schilddruse Diagnostik und Therapie ihrer Krankheiten. Springer Ver lag Berlin Heidelberg *New York, 1969 159 pages, 25 figures Price* DM 38

A short textbook on the diseases of the thyroid gland by one of the leading specialists on the continent. The present book is to be regarded as a synopsis of a standard text book by Oberdis & Klein Die Krankheiten der *Schilddruse Georg Thieme* Verlag Stuttgart, 1967

It is fluid written with special emphasis on differential diagnosis and therapy A *seperate* chapter has been reserved ophthalmic pathology with several illustrative photographs Selected *references* mainly German can be found at the end of the book

The bo k can be recommended as an excellent survey on the *present stage* of diag nos s and management of an endocrine entity with prominent ophthalm logic signs

Niels Willumsen

Michi ls J L Humeur *aqueuse et la barriere* hematocamerulaire Bruxelles Albert de Visscher 1968 Pg 242

Since the Rapp Soc Franç Ophtalm 1955 L Humeure aqueuse et ses fonctions by Amsler Verrey and Huber this appears the *most* elaborate presentation of the topic. A first pa t d als with the formation composition and *exchange* of the aqueous

The sec nd part represents an interesting study of the problem of th*e incoagulability* of the hyphema

In the thi d pa the cytology in cases of uveal pathology is considered The final fourth part deals with the appearence of *tumorcells* and an increase of transaminases *in* the aque us accompanying mal gnant intraocular growths

The b k is *recommended* because of its didactic arrangements of the interesting ma te al

P Brændstrup

Proceedings in Echo Encephalography Edited by E. Kazner W Schiefer and K. J *Zulch* Springer Verlag Berlin Heidelberg New York 1968 253 pages 278 fi gures DM 68 US $ 17

An *internati nal* symposion on Echo Encephalography was held in Erlangen april 1967 The editors have *collected* the contribut ons – all printed in English – in this wonder fully equipped book with many illustrations

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Coding system for disorders of the eye

Written by J Schappert Kimmijser A. Colenbrander and S Franken Published by the International Council of Ophthalmology and the International Federation of Ophthalmological Societies Edited by S Karger Basel (Switzerland)

The present trend of scientific development will in time make coding of the data obtained inevitable In ophthalmology the necessity of a good coding system is becoming increasingly apparent both for scientific research at national and international levels as for statistical work in Ophthalmological Departments Several attempts have been made in the past to achieve a serviceable coding system but no system was completely satisfactory Either the system was too complicated comprising too many digits or it did not offer enough scope for detailed codification of ophthalmological data The latter disadvantage applies to the codification of eye diseases in the International Classification of Diseases (I C D) published by the W H O which fails to provide adequate details of eye conditions so that much important information is lost

A good coding system for eye conditions must be logically set up systematic on the one hand and on the other hand it must follow as closely as possible the course by which a diagnosis is reached In addition it must be easy to use and not take up too many digits

The Coding System for Disorders of the Eye published by the International Council of Ophthalmology in 1968 fulfils these criteria It is a six digit system subdivised into 13 anatomical and 4 functional groups to which a separate group of syndroms has been added As in an ophthalmological diagnosis the site of the lesion is nearly always known the type of lesion is usually known, but the cause is often unknown the subdivision of the anatomical group are in this order i e the first two digits refer to the site of the lesion the third and fourth to the type of lesion and the fifth and sixth to the aetiology

The system also offers scope for additions and extensions It can also if desired be included in the I C D of the W H O The chapter Con iderations and Basic Principles p eceding the tables and index, gives more information on this and many other p ints

If the user studies the tables before beginning to codify he will appreciate both the principles of the system and the opportunities which it offers A detailed alphabetical index of eye d sorders with their code numbers suitable for international use is inten led t make the use of the coding system easier

Prix International Paul Reiss 1970
Fondé par F et C Wolff sous le patronage de la Société Française d'Ophtalmologie

Nous appelons aux candidats que leurs travaux (10 exemplaires dactylographiés en français ou en angla s) doivent être adresses au Secrétaire Général de la *Société Fran ai e d'Ophtalm l gie* 98 rue de Charenton à Paris (1) *avant le 31 decembre 1969 dernier d lai*

The bulk of the book concerns expiriences with A scan (31 contributions) but also B scan and echo pulsations are dealt with Some overlapping inevitably occurs in a book of this kind but it must be regarded as a valuable up to date aid in neurosurgical departments employing ultrasound

The special problem in this field is the strong absorption of ultrasound in the bony skull in connection with the deep position of the structures to be examined This makes the practical considerations quite different from those in ophthalmological ultrasound diagnosis – The book therefore cannot be recommended for ophthalmologists

H Fledelius

Coding system for disorders of the eye

Written by J Schappert Kimmijser A Colenbrander and S Franken Published by the International Council of Ophthalmology and the International Federation of Ophthalmological Societies Edited by S Karger Basel (Switzerland)

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III International Ergophthalmological Symposium

On occasion of the XXI International Congress of Ophthalmology the Internati Association for Ergophthalmology plans to hold its III Symposium about Problem Occupational Medicine in Ophthalmology

Registrations for participation and for scientific contributions are kindly asked to forwarded at your earliest convenience but not later than Dec 1st 1969 to the lowing address

Prof Dr H J Merte Direktor der Augenklinik rechts der Isar der Technisc Hochschule Munchen
D – 8000 Munchen 80 Ismaniger Strasse 22

13 Jahreshauphversammlung der Österreichischen Ophthalmologische Gesellschaft in Gra 4–7 Juni 1970

Anfragen und Anmeldungen sind an Doz Dr W Funder erbeten Wiener Medizinis Akademie fur arztliche Fortbildung Spitalgasse 2 A 1090 Wien IX Österrei Sprechzeit Vorträge 10 Minuten Mitteilungen und Demonstrationen 6 Minuten A meldeschluss fur wissenschaftliche Beitrage 1 Marz 1970

The First International Symposium on Plastic and Reconstructive Surgery of the Face and Neck

will be held August 9 through 14 1970 at the Waldorf Astoria Hotel in New York Cit

To further information contact

John Conley M D 139 E 36th Street New York is general chairman of the International Symposium